

Changes have been made to this item. Details of the corrigendum are at the end of this document.

## **7.05 TIRZEPATIDE,**

**Solution for injection 2.5 mg in 0.5 mL vial/pre-filled pen,**

**Solution for injection 5 mg in 0.5 mL vial/pre-filled pen,**

**Solution for injection 7.5 mg in 0.5 mL vial/pre-filled pen,**

**Solution for injection 10 mg in 0.5 mL vial/pre-filled pen,**

**Solution for injection 12.5 mg in 0.5 mL vial/pre-filled pen,**

**Solution for injection 15 mg in 0.5 mL vial/pre-filled pen**

**Mounjaro®**

**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 (Written) listing as dual therapy in combination with metformin for the treatment of adult patients with inadequately controlled type 2 diabetes mellitus (T2DM) who (i) have comorbid severe obesity or (ii) identify as Aboriginal and Torres Strait Islander.
- 1.2 The resubmission claimed there is a high, unmet need for superior treatment options in high-risk groups of patients with type 2 diabetes.
- 1.3 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	<p><del>Patients with inadequately controlled type 2 diabetes, who meet specific prior therapy criteria<sup>a</sup></del></p> <ul style="list-style-type: none"> <li>• Patients with inadequately controlled type 2 diabetes <u>with BMI <math>\geq 35</math> kg/m<sup>2</sup></u>, who meet specific prior therapy criteria<sup>b</sup></li> <li>• <u>Aboriginal and Torres Strait Islander peoples with inadequately controlled type 2 diabetes, who meet specific prior therapy criteria<sup>b</sup></u></li> </ul>
Intervention	Tirzepatide 5 mg, 10 mg or 15 mg subcutaneous injection once weekly
Comparator	Semaglutide 0.5 mg or 1.0 mg subcutaneous injection once weekly
Outcomes	Improved glycaemic control and body weight management leading to reduced macrovascular and microvascular complications, and associated morbidity and mortality associated with these complications <sup>c</sup>
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 1.0 mg once weekly, when used in dual therapy with metformin.

Source: Table 1.2-1, p8 of the resubmission

Abbreviations: BMI, body mass index

Note: Key changes compared to the July 2023 submission are marked using underline and ~~strike through~~

<sup>a</sup> The target population was based on a draft restriction for GLP-1 RAs in the DUSC Report 2023. In March 2023, the PBAC recommended that the use of GLP-1 RAs should be restricted to patients who are contraindicated, intolerant or inadequately responsive to SGLT2 inhibitors. At the time, the PBAC noted that further consultation will be conducted on the wording of the restriction.

<sup>b</sup> The condition must be inadequately responsive to at least one of: metformin, a sulfonylurea, insulin; and the patient must be contraindicated, intolerant or did not achieve a clinically meaningful glycaemic response with an SGLT2 inhibitor.

<sup>c</sup> Trial outcomes included: HbA1c, weight, other biomarkers, quality of life and adverse events.

### 2 Background

#### Registration status

- 2.1 The TGA approved tirzepatide (pre-filled pens) 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 TGA approval is currently in place for the three presentations that are being requested for listing on the PBS (single-use vial, single-use pre-filled pen and multi-dose pre-filled pen).
- 2.3 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):
- $\geq 30 \text{ kg/m}^2$  (obesity) or
  - $\geq 27 \text{ kg/m}^2$  to  $< 30 \text{ kg/m}^2$  (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes or type 2 diabetes mellitus).

### ***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 the treatment of adult patients with inadequately controlled type 2 diabetes as dual therapy in combination with metformin.
- 2.5 The PBAC did not recommend tirzepatide for the requested listing. The PBAC considered that the claim of superior effectiveness was reasonable for tirzepatide 5 mg versus semaglutide 0.5 mg. The PBAC considered that tirzepatide 10 mg and 15 mg were superior in terms of glycaemic benefits and short-term weight loss compared to semaglutide 1 mg, but this claim was not supported for tirzepatide 5 mg versus semaglutide 1 mg. The PBAC considered the non-inferior safety claim was inadequately supported for any of the comparisons (para 7.1 and 7.10, tirzepatide Public Summary Document (PSD), July 2023 PBAC meeting).
- 2.6 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 (ICER) 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 PSD, July 2023 PBAC meeting).
- 2.7 The PBAC noted comments from various stakeholders that highlighted the benefits of tirzepatide treatment and the importance of having multiple therapeutic options given the supply shortages. The PBAC specifically was sympathetic to the notion that glucagon-like peptide-1 (GLP-1) analogues and tirzepatide be listed on the PBS for Aboriginal and Torres Strait Islander peoples under a Streamlined Authority for those with type 2 diabetes or pre-diabetes with obesity with no further restrictions. The PBAC stated that it would welcome a proposal to address the needs of this higher risk

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group of patients in a future resubmission (para 7.3, tirzepatide PSD, July 2023 PBAC meeting).

2.8 Table 2 presents a summary of PBAC’s previous advice for a resubmission and how this resubmission addressed them.

**Table 2: Summary of key matters of concern**

Matter of concern (July 2023 PBAC meeting)	How the resubmission addresses it (November 2024 PBAC meeting)
<b>Context</b>	
One repeat would be most appropriate for titration doses of tirzepatide (2.5 mg, 7.5 mg and 12.5 mg) (para 7.5).	The same number of repeats (5) is requested for all tirzepatide doses. The resubmission argued that treatment duration at titration doses should not be limited to 8 weeks and that patients who experience tolerability issues may undergo slower titration.
Clinicians would likely want to use tirzepatide in combination with sulfonylurea or insulin given available clinical data within the type 2 diabetes trial program (para 7.5).	The requested listing of tirzepatide is for use as dual therapy in combination with metformin only. The resubmission claimed, based on expert opinion, that the aim when initiating tirzepatide is to reduce medication burden for patients by stopping sulfonylureas and down-titrating or ceasing insulin.
There is high risk of use beyond the proposed restriction that limited tirzepatide use as dual therapy with metformin only (para 7.5).	The revised listing remains for use as dual therapy with metformin only in a narrower population, with a higher authority level (Written Authority), treatment initiation limited to endocrinologists only, and new continuing treatment criteria based on glycaemic response.
<b>Clinical evidence</b>	
The comparison of low dose tirzepatide (5 mg) versus high dose semaglutide (1 mg) was relevant given the proposed price for low dose tirzepatide was higher than proposed for high dose semaglutide (para 7.7). Increased adverse events associated with higher doses of tirzepatide (10 mg and 15 mg) may limit titration to these doses in practice (para 7.11).	The resubmission argued that the comparison of low dose tirzepatide versus high dose semaglutide is less relevant given the target population are of higher risk and are more likely to require titration to the higher doses of tirzepatide to achieve their treatment goals. Consequently, the low dose of tirzepatide was considered a temporary dose. The resubmission maintains that the most relevant comparisons for tirzepatide versus semaglutide are within each dose-escalation step and the proposed tiered pricing structure complements these dose comparisons. The ESC noted the price of tirzepatide 5 mg dose remains higher than semaglutide 1 mg.
The long-term comparative efficacy of tirzepatide is unknown, with only short-term data from the key trial (40 weeks). The clinical relevance of change in HbA1c may shift in the context of changing treatment algorithms based on patient-centred outcomes. Furthermore, there was a lack of data supporting reductions in downstream complications associated with short-term weight loss (para 7.10).	No long-term data were presented.

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Matter of concern (July 2023 PBAC meeting)	How the resubmission addresses it (November 2024 PBAC meeting)
<b>Economic evaluation</b>	
The PBAC considered the submission's assumptions regarding modelled circumstances of use were unlikely to reflect Australian clinical practice (fixed dosing of GLP-1 RA/GIP and insulin therapies, perfect persistence, insulin intensification at HbA1c > 7.5% and no concomitant use of GLP-1 RA and insulin therapies). The PBAC considered that in practice, the threshold for conversion to insulin would likely be at least 8.0% due to patients' reluctance to commence insulin (para 7.13).	The resubmission's model maintains fixed dosing of GLP-1 RA/GIP and insulin therapies and perfect persistence. The insulin intensification threshold has been reduced to HbA1c >7.0%, which the resubmission claimed is consistent with the proposed restriction for continuing tirzepatide treatment, PBS restrictions for use of medicines in combination with insulin, and clinical guidelines. The resubmission's model maintains no concomitant use of GLP-1 RA and insulin therapies.
The approach used to apply weight-based utility/disutility values was considered unreliable (para 7.15)	The resubmission maintains the approach to weight-related utilities; claiming that the first year utility gain associated with weight loss and subsequent utility loss for patients with BMI >25 kg/m <sup>2</sup> are independent changes, and the baseline utility used in the model is unlikely to reflect the utility of patients with a BMI ≥35 kg/m <sup>2</sup> .
Constant eGFR treatment effects should be incorporated (para 7.16).	Constant eGFR treatment effects have been included.
UKPDS drift should be used for all biomarkers (para 7.16).	UKPDS drift has been included for some biomarkers only.
The hypoglycaemia disutility should be reduced to 0.003 per event (para 7.16).	The hypoglycaemia disutility has been reduced to 0.003.
A substantial price reduction that results in an ICER in the order of \$30,000 per QALY would be required for the proposed listing to be considered cost-effective (para 7.16).	The resubmission argued that the proposed population is at greater risk of experiencing life-threatening diabetes-related complications, there is a high unmet need in this population for effective treatment options like tirzepatide, and it is appropriate to consider a higher ICER of \$ <sup>1</sup> for tirzepatide 15 mg versus semaglutide 1.0 mg. The proposed tiered pricing of tirzepatide includes lower prices for tirzepatide 5 mg and 10 mg but a higher price for tirzepatide 15 mg compared to the flat pricing of tirzepatide in the July 2023 submission.
<b>Utilisation and financial impact of listing</b>	
The PBAC noted concerns regarding the use of historical growth trends of GLP-1 analogues to estimate the utilisation and financial implications of a tirzepatide listing given recent recommendations to narrow eligibility of such therapies (para 7.17).	Revised financial estimates were presented to account for the narrower target population, with substantial changes to methods and data inputs. The ESC noted that the estimated tirzepatide utilisation had more than doubled with the net cost to the PBS/RPBS over 6 years increasing from \$ <sup>2</sup> to \$ <sup>2</sup> in the resubmission.
Additional sensitivity analyses may assist in understanding some of the uncertainty regarding future growth in GLP-1 analogue use (para 7.17).	Sensitivity analyses were presented for key assumptions used in the budget impact analysis.
The financial impact was uncertain and extremely high at the requested price (para 7.17).	A revised price structure was proposed based on the outcomes of the economic model.

Source: Table 4-1, p260 of the resubmission; Tirzepatide Public Summary Document, July 2023 PBAC meeting

Abbreviations: eGFR, estimated glomerular filtration rate; 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; QALY, quality adjusted life year; UKPDS, UK Prospective Diabetes Study

The redacted values correspond to the following ranges

1 \$35,000 to < \$45,000

2 > \$1 billion

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 in the restriction proposed by the submission (Option 1). The Secretariat also provided additional restrictions combining the 2 different patient populations: BMI ≥35 kg/m<sup>2</sup> and ATSI (Option 2).

#### Option 1 as proposed by the submission (separate listings for the 2 different patient populations: BMI ≥35 kg/m<sup>2</sup> and ATSI)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands	
TIRZEPATIDE							
tirzepatide 2.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1	Mounjaro	
tirzepatide 5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1		
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1		
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 2.5 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1		
tirzepatide 5 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1		
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	<del>5</del> 1		
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use vials	NEW	\$ [redacted] published effective	1	4	5		
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	<del>5</del> 1		
tirzepatide 5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5		
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	<del>5</del> 1		
tirzepatide 10 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5		
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	<del>5</del> 1		

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tirzepatide 15 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ <del>145</del> published effective	1	1	5	
<b>Restriction Summary [new 1] / Treatment of Concept: [new 2]</b>						
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)						
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners						
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required In Writing (only via mail/postal service or electronic upload to Hobart (HPOS));						
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.						
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.						
<b>Administrative Advice:</b> Special Pricing Arrangements apply.						
<b>Indication:</b> Diabetes mellitus type 2 <del>and comorbid severe obesity</del>						
<b>Treatment Phase:</b> Initial treatment in patients with comorbid severe obesity						
<b>Clinical criteria:</b>						
Patient must have a confirmed diagnosis of type 2 diabetes						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must have a Body Mass Index greater ( <i>BMI</i> ) than or equal to 35 kg/m <sup>2</sup>						
<b>AND</b>						
<b>Clinical criteria:</b>						
The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin						
<b>AND</b>						
<b>Clinical criteria:</b>						
The condition must be inadequately responsive to at least one of: (i) metformin, (ii) a sulfonylurea, or (iii) insulin						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor; OR						
Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must not receive more than 24 weeks of treatment under this restriction						
<b>Treatment criteria:</b>						
Must be treated by an endocrinologist						
<b>Treatment criteria:</b>						
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						
<b>Population criteria:</b>						
Patient must be at least 18 years of age <del>18 years of age or older.</del>						
<b>Prescribing Instructions:</b>						
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'.						

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	<p><b>Administrative Advice:</b>  <b>Prescribing instructions:</b>                  The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> <li>(a) <del>a completed authority prescription form</del> details of the proposed prescription(s); and</li> <li>(b) <del>a completed Type 2 Diabetes Mellitus PBS Authority Application – Supporting Information Form which includes the following:</del> a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</li> <li>(c) <del>a copy of the HbA1c pathology results which must be no greater</del> no more than 4 months old (or if using portable HbA1c point of care testing (PoCT), <del>a photograph</del> the meter reading alongside and the result date, <del>patient's full name and Medicare ID number must be provided</del>)</li> <li>(d) details of prior SGLT2 inhibitor therapy (i.e. confirmation of either (i) inadequate responsiveness; (ii) intolerance, or (iii) contraindication)</li> <li>(e) details of prior metformin, sulfonylurea, or insulin therapy</li> <li>(f) a measurement of body weight, height, and BMI at the time of application (no more than 1 month old)</li> </ul>
	<p><b>Prescribing Instructions:</b>  <b>Administrative Advice:</b>                  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:</p> <ul style="list-style-type: none"> <li>(a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies),</li> <li>(b) Red cell transfusion within the previous 3 months.</li> </ul>
	<p><b>Administrative Advice:</b>                  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</p>
	<p><b>Administrative Advice:</b>                  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.</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TIRZEPATIDE						
tirzepatide 2.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5 1	Mounjaro
tirzepatide 5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5 1	
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	

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tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5 1
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5
tirzepatide 2.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5 1
tirzepatide 5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5
tirzepatide 7.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5 1
tirzepatide 10 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5
tirzepatide 12.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5 1
tirzepatide 15 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5 1
tirzepatide 5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5 1
tirzepatide 10 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5 1
tirzepatide 15 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5

**Restriction Summary [new 1] / Treatment of Concept: [new 2]**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required in Writing (only via mail/postal service or electronic upload to Hobart (HPOS));	
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.	
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.	
<b>Administrative Advice:</b> Special Pricing Arrangements apply.	
<b>Indication:</b> Diabetes mellitus type 2 in an Aboriginal and Torres Strait Islander Adult	
<b>Treatment Phase:</b> Initial treatment in an Aboriginal or Torres Strait Islander patients	
<b>Clinical criteria:</b>	
Patient must have a confirmed diagnosis of type 2 diabetes	
<b>AND</b>	
<b>Clinical criteria:</b>	
Patient must be an Aboriginal and Torres Strait Islander person Patient must identify as Aboriginal or Torres Strait Islander.	
<b>AND</b>	

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	<b>Clinical criteria:</b>
	The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be inadequately responsive to at least one of: (i) metformin, (ii) a sulfonylurea, or (iii) insulin
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor; OR
	Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>Patient must not receive more than 24 weeks of treatment under this restriction</del>
	<b>Treatment criteria:</b>
	Must be treated by an endocrinologist
	<b>Treatment criteria:</b>
	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
	<b>Population criteria:</b>
	<del>Patient must be at least 18 years of age 18 years of age or older.</del>
	<b>Prescribing Instructions:</b> 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'.
	<del><b>Administrative Advice:</b></del> <b>Prescribing instructions:</b> The authority application must be made in writing and must include: <ul style="list-style-type: none"> <li>(a) <del>a completed authority prescription form</del> details of the proposed prescription(s); and</li> <li>(b) <del>a completed Type 2 Diabetes Mellitus PBS Authority Application – Supporting Information Form which includes the following:</del> a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</li> <li>(c) <del>a copy of the HbA1c pathology results which must be no greater</del> no more than 4 months old (or if using portable HbA1c point of care testing (PoCT), <del>a photograph</del> the meter reading alongside and the result date, <del>patient's full name and Medicare ID number must be provided</del>)</li> <li>(d) details of prior SGLT2 inhibitor therapy (i.e. confirmation of either (i) inadequate responsiveness; (ii) intolerance, or (iii) contraindication)</li> <li>(e) details of prior metformin, sulfonylurea, or insulin therapy</li> <li>(f) Confirmation of Aboriginal and Torres Strait Islander people identity as documented by a CTG code on Medicare card</li> </ul>

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	<p><b>Prescribing Instructions:</b></p> <p><b>Administrative Advice:</b></p> <p>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.</p> <p>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.</p>
	<p><b>Administrative Advice:</b></p> <p>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</p>
	<p><b>Administrative Advice:</b></p> <p>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.</p>

**Option 2 as suggested by the secretariat (combining the 2 different patient populations: BMI ≥35 kg/m<sup>2</sup> and ATSI)**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TIRZEPATIDE						
tirzepatide 2.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	1	Mounjaro
tirzepatide 5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	1	
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	1	
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 2.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	1	
tirzepatide 5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5	
tirzepatide 7.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	1	
tirzepatide 10 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5	

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tirzepatide 12.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	1
tirzepatide 15 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	5
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	1
tirzepatide 5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	1
tirzepatide 10 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	1
tirzepatide 15 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$ [redacted] published effective	1	1	5

**Restriction Summary [new 1] / Treatment of Concept: [new 2]**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required in Writing (only via mail/postal service or electronic upload to Hobart (HPOS));	
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.	
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.	
<b>Administrative Advice:</b> Special Pricing Arrangements apply.	
<b>Indication:</b> Diabetes mellitus type 2	
<b>Treatment Phase:</b> Initial treatment	
<b>Clinical criteria:</b>	
Patient must have a Body Mass Index greater (BMI) than or equal to 35 kg/m <sup>2</sup> ; OR	
Patient must identify as Aboriginal or Torres Strait Islander.	
<b>AND</b>	
<b>Clinical criteria:</b>	
The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin	
<b>AND</b>	
<b>Clinical criteria:</b>	
The condition must be inadequately responsive to at least one of: (i) metformin, (ii) a sulfonylurea, or (iii) insulin	
<b>AND</b>	
<b>Clinical criteria:</b>	
Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor; OR	
Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor	
<b>Treatment criteria:</b>	
Must be treated by an endocrinologist	
<b>Treatment criteria:</b>	

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	<i>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</i>
	<b>Population criteria:</b>
	<i>Patient must be at least 18 years of age</i>
	<b>Prescribing Instructions:</b> <i>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'.</i>
	<b>Prescribing instructions:</b> <i>The authority application must be made in writing and must include:</i> <ul style="list-style-type: none"> <li>(a) details of the proposed prescription(s); and</li> <li>(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</li> <li>(c) the HbA1c pathology results which must be no more than 4 months old (or if using portable HbA1c point of care testing (PoCT), the meter reading and the result date, must be provided)</li> <li>(d) details of prior SGLT2 inhibitor therapy (i.e. confirmation of either (i) inadequate responsiveness; (ii) intolerance, or (iii) contraindication)</li> <li>(e) details of prior metformin, sulfonylurea, or insulin therapy</li> <li>(f) For patients with BMI greater than or equal to 35 kg/m<sup>2</sup>, a measurement of body weight, height, and BMI at the time of application (no more than 1 month old) must be provided.</li> </ul> <i>For Aboriginal or Torres Strait Islander patients, confirmation of Aboriginal and Torres Strait Islander people identity as documented by a CTG code on Medicare card must be provided.</i>
	<b>Administrative Advice:</b> <i>Definition:</i> <i>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.</i> <i>Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies:</i> <ul style="list-style-type: none"> <li>(a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies),</li> <li>(b) Red cell transfusion within the previous 3 months.</li> </ul>
	<b>Administrative Advice:</b> <i>Abbreviations used in the restriction are as follows:</i> 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
	<b>Administrative Advice:</b> <i>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.</i>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
TIRZEPATIDE						
tirzepatide 2.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [REDACTED] published effective	1	4	1	Mounjaro

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tirzepatide 5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$█ published effective	1	4	3
tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$█ published effective	1	4	1
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$█ published effective	1	4	3
tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$█ published effective	1	4	1
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$█ published effective	1	4	3
tirzepatide 2.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	1
tirzepatide 5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	3
tirzepatide 7.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	1
tirzepatide 10 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	3
tirzepatide 12.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	1
tirzepatide 15 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	3
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	3
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 10 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	3
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 15 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	3
<b>Restriction Summary [new 1] / Treatment of Concept: [new 2]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/electronic)					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Indication:</b> Diabetes mellitus type 2					

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	<b>Treatment Phase:</b> <i>First continuing treatment – until the assessment of response</i>
	<b>Clinical criteria:</b>
	<i>Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition under the initial treatment restriction; OR</i>
	<i>Patient must have received PBS-subsidised treatment with this drug for this condition under the grandfather treatment restriction that is insufficient to complete the first 40 weeks of treatment</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have demonstrated a response to treatment with this drug as determined by the treating clinician.</i>
	<b>Treatment criteria:</b>
	<i>Must be treated by an endocrinologist</i>
	<b>Treatment criteria:</b>
	<i>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</i>
	<b>Prescriber instructions:</b> <i>This treatment phase provides additional 16 weeks of initial treatment until assessment of response is conducted after a total of 40 weeks of initial treatment.</i>
	<b>Administrative Advice:</b> <i>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</i>
	<b>Administrative Advice:</b> <i>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.</i>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
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tirzepatide 7.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	1	
tirzepatide 10 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 12.5 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	1	
tirzepatide 15 mg/0.5 mL injection, 4 x 0.5 mL single-use pen devices	NEW	\$ [redacted] published effective	1	4	5	
tirzepatide 2.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$ [redacted] published effective	4	4	1	

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tirzepatide 5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	5
tirzepatide 7.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	1
tirzepatide 10 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	5
tirzepatide 12.5 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	1
tirzepatide 15 mg/0.5 mL injection, 0.5 mL single-use vial	NEW	\$█ published effective	4	4	5
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	5
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 10 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	5
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	1
tirzepatide 15 mg/0.6 mL injection, 2.4 mL multi-dose pen device	NEW	\$█ published effective	1	1	5

**Restriction Summary [new 1] / Treatment of Concept: [new 2]**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required In Writing (only via mail/postal service or electronic upload to Hobart (HPOS));	
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.	
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.	
<b>Administrative Advice:</b> Special Pricing Arrangements apply.	
<b>Indication:</b> Diabetes mellitus type 2	
<b>Treatment Phase:</b> Subsequent continuing treatment	
<b>Clinical criteria:</b>	
Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition under the first continuing treatment OR	
Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition under the grandfather arrangements if adequate response is achieved after 40 weeks of initial treatment	
<b>AND</b>	
<b>Clinical criteria:</b>	
Patient must have demonstrated an adequate response to treatment with this drug for this condition	
<b>Treatment criteria:</b>	
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	

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	<p><b>Prescribing instructions:</b>  <i>The authority application must be made in writing and must include:</i></p> <ul style="list-style-type: none"> <li>(a) <i>details of the proposed prescription(s); and</i></li> <li>(b) <i>a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</i></li> <li>(c) <i>HbA1c pathology results which must be no more than 1 month old (or if using portable HbA1c point of care testing (PoCT) the meter reading and the result date, if it was not provided before.</i></li> </ul>
	<p><b>Administrative Advice:</b>  An adequate response to treatment is defined as:</p> <ul style="list-style-type: none"> <li>(a) a HbA1c measurement of less than 7% or</li> <li>(b) a HbA1c reduction of at least 2.0% from baseline.</li> </ul>
	<p><b>Administrative Advice:</b>  <i>Abbreviations used in the restriction are as follows:</i>  SGLT2 - <i>sodium glucose transporter-2 inhibitor (drug names ending in 'flozin')</i>  DPP4 - <i>dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin')</i>  GLP-1 - <i>glucagon-like peptide-1 receptor agonist</i></p>
	<p><b>Administrative Advice:</b>  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.</p>
	<b>Indication:</b> Diabetes mellitus type 2
	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised treatment- Grandfather arrangement
	<b>Clinical criteria:</b>
	Patient must have been receiving non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date].
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have had a Body Mass Index greater (BMI) than or equal to 35 kg/m<sup>2</sup> prior to initiating treatment with this drug OR</i>
	<i>Patient must identify as Aboriginal or Torres Strait Islander.</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>The condition must have been inadequately responsive to at least one of: (i) metformin, (ii) a sulfonylurea, or (iii) insulin</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor prior to initiating treatment with this drug; OR</i>
	<i>Patient must have had a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor prior to initiating treatment with this drug</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have demonstrated an adequate response to treatment with this drug for this condition if received 40 weeks of therapy.</i>

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	<b>Treatment criteria:</b>
	Must be treated by an endocrinologist
	<b>Treatment criteria:</b>
	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
	<b>Population criteria:</b>
	Patient must be at least 18 years of age
	<b>Administrative Advice:</b> 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.
	<b>Administrative Advice:</b> An adequate response to treatment with this drug is defined as: (a) a HbA1c measurement of less than 7% or (b) a HbA1c reduction of at least 2.0% from baseline.
	<b>Administrative Advice:</b> 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
	<b>Administrative Advice:</b> 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.
	<b>Prescribing instructions:</b> The authority application must be made in writing and must include: (a) details of the proposed prescription(s); and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). (c) the HbA1c pathology results at baseline, prior initiating non-PBS subsidised treatment. (d) details of prior SGLT2 inhibitor therapy (i.e. confirmation of either (i) inadequate responsiveness; (ii) intolerance, or (iii) contraindication) (e) details of prior metformin, sulfonylurea, or insulin therapy (f) for patients with BMI greater than or equal to 35 kg/m <sup>2</sup> , a measurement of body weight, height, and BMI at baseline must be provided. (g) for Aboriginal or Torres Strait Islander patients, confirmation of Aboriginal and Torres Strait Islander people identity as documented by a CTG code on Medicare card must be provided. (h) the HbA1c pathology results assessing the response to treatment if patients received 40 weeks of treatment. The result must be no more than 1 month old.

3.2 The resubmission requested a special pricing arrangement consisting of tiered effective prices based on the following rebates on published prices: [REDACTED] % for 2.5 mg and 5 mg doses, [REDACTED] % for 7.5 mg and 10 mg doses and [REDACTED] % for 12.5 mg and 15 mg doses. Compared to the proposed effective price in the previous submission (flat

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effective DPMQ of \$ [REDACTED] for all doses), the current proposed effective prices represent a [REDACTED]% reduction for 2.5 mg and 5 mg doses, a [REDACTED]% reduction for 7.5 mg and 10 mg doses and a [REDACTED]% increase for the 12.5 mg and 15 mg doses. As such, the resubmission proposed effective DPMQs of \$ [REDACTED] for 2.5 mg and 5 mg doses, \$ [REDACTED] for the 7.5 mg and 10 mg doses, and \$ [REDACTED] for the 12.5 mg and 15 mg doses. The pre-PBAC response offered a price reduction with effective DPMQs of \$ [REDACTED] for the 2.5 mg and 5 mg doses, \$ [REDACTED] for the 7.5 mg and 10 mg doses, and \$ [REDACTED] for the 12.5 mg and 15 mg doses. In addition, the pre-PBAC response stated that, if recommended, the sponsor would be requesting the listings of only two presentations: the multi-dose pen device and the single-use vial.

- 3.3 The resubmission noted that special pricing arrangements are currently in place for semaglutide and dulaglutide.
- 3.4 The ESC considered the proposed restrictions were very complex, and likely to be burdensome for prescribers and may result in prescribing errors. The multiple treatment phases (initial, balance of supply and continuing) with an array of doses (all with separate item codes), with script coverage based on initial treatment response assessed at 40 weeks and every 24 weeks thereafter. It is unclear how this could be practically implemented to align with a flexible titration approach using the recommended titration algorithm in the Product Information. The ESC advised that the restrictions should be simplified. The pre-PBAC response proposed a number of amendments to the restrictions put forward in the resubmission, including the removal of the balance of supply treatment phase. The additional amendments proposed are outlined in paragraphs 3.5, 3.9, 3.13, 3.14 and 3.15.
- 3.5 The PBAC previously considered that one repeat would be most appropriate for the 2.5 mg, 7.5 mg and 12.5 mg dose strengths of tirzepatide which are used for titration purposes only (para 7.5, tirzepatide PSD, July 2023 PBAC meeting). The resubmission requested 5 repeats for the titration doses, claiming that patients with tolerability issues may undergo slower titration and that limiting the maximum duration to 8 weeks may increase burden to patients and clinicians, particularly those in rural or remote settings. The ESC considered that there is a need for more flexible dose titration in clinical practice than the 4-week period in the key trial. However, the ESC considered the request for 5 repeats for dose titration was not reasonable as clinicians should review patients during dose titration and further doses prescribed as appropriate. The ESC considered there was limited evidence to support how dose titration would occur in clinical practice. The pre-PBAC response proposed the number of repeats for the 2.5 mg, 7.5 mg and 12.5 mg doses be reduced from 5 to 1.
- 3.6 The proposed PBS restriction (type 2 diabetes and BMI  $\geq 35$  kg/m<sup>2</sup> or Aboriginal and Torres Strait Islander peoples with type 2 diabetes) is narrower than the approved TGA indication, key trial population, the requested restriction in the July 2023 submission and the current GLP-1 RA restriction.

- 3.7 The resubmission stated that the targeting of treatment to the defined high-risk subgroups was in response to PBAC advice. The proposed population is narrower than populations previously considered appropriate by the PBAC in July 2023. The evaluation and the ESC considered it was unclear whether the proposed eligible population represents the most appropriate targeted use of tirzepatide noting its proposed place in therapy as an alternative to GLP-1 RAs and clinical evidence in broader populations through its trial program.
- 3.8 The resubmission proposed a BMI threshold of 35 kg/m<sup>2</sup> to define patients with severe obesity. The PBAC has previously stated that BMI criteria should be adjusted for, at a minimum, Asian and Aboriginal and Torres Strait Islander populations (para 7.4, semaglutide PSD, March 2022 PBAC meeting). Adjustments for these populations are typically applied as a 2.5 kg/m<sup>2</sup> reduction on BMI thresholds. The ESC considered an adjusted BMI threshold for the aforementioned populations would be more appropriate.
- 3.9 The resubmission claimed that the target population will likely present with more complex disease, multiple comorbidities and highly uncontrolled diabetes. Therefore, it is expected that these patients will be managed by endocrinologists, which would ensure adequate assessment of these patients prior to commencing therapy. The Pre-Sub-Committee Response (PSCR) raised that an alternative option may be that the patient must be under the care of or in consultation with an endocrinologist. The ESC considered a high proportion of people with type 2 diabetes are managed by GPs who would manage medication initiated by another specialist. The ESC considered the requirement for initial prescribing by an endocrinologist would be a barrier to tirzepatide access as access to endocrinologists vary across Australia. The ESC considered this requirement could hinder access for Aboriginal and Torres Strait Islander peoples, however some ACCHOs have may have access to endocrinologists through in-reach specialist services. The ESC advised that the group of eligible prescribers should be broadened and could potentially require initial prescribing occur in consultation with an endocrinologist. The pre-PBAC response proposed that the criterion requiring patients to be under the treatment of an endocrinologist could be amended to 'under the care of or in consultation with an endocrinologist.'
- 3.10 Based on the proposed restriction, patients would require up to 6 visits to endocrinologists during the initial titration period (up to 40 weeks) to achieve the maximum 15 mg dose.
- 3.11 The resubmission noted that the Written Authority level and required documentation for initial treatment is substantially more stringent than the current GLP-1 RA restriction; however, this was necessary to reduce the risk of use outside the proposed restriction. The evaluation and the ESC noted the administrative requirements, which include provision of recent HbA1c pathology results ( $\leq 4$  months old for initial scripts and  $\leq 1$  month old for continuing scripts), appear burdensome, and processing of information may be beyond the current capacity of the health system, and would likely hinder access to treatment.

- 3.12 The proposed restriction is intended for tirzepatide as dual therapy with metformin. The ESC highlighted that this excludes patients who cannot use metformin.
- 3.13 GLP-1 RAs can be used as dual or triple therapy in combination with metformin, a sulfonylurea and/or insulin. The PBAC previously stated that clinicians would likely want to use tirzepatide in combination with sulfonylurea or insulin given available clinical data within the trial program. The PBAC also considered the high risk of use beyond the proposed restriction given tirzepatide would be limited to use as dual therapy with metformin only (para 7.5, tirzepatide PSD, July 2023 PBAC meeting). The PSCR considered use as dual therapy with metformin was appropriate as expert advice and clinical guidelines advise against the use of sulphonylureas as second line therapy and people with comorbid obesity are highly unlikely to use a sulphonylurea or insulin prior to using an SGLT2i or tirzepatide because sulphonylureas and insulin can cause weight gain and hypoglycaemia. The ESC reaffirmed PBAC's previous advice that clinicians would want the option to use tirzepatide in combination with sulfonylurea or insulin. The ESC noted the PSCR stated that the sponsor may make a future submission for use with insulin. The ESC encouraged a submission to address co-prescribing with insulin or sulfonylurea to address the inconsistencies with expectations in clinical practice. The pre-PBAC response proposed including use in combination with a sulfonylurea, which the response stated will ensure patients who cannot use metformin have access to tirzepatide treatment (see paragraph 3.12).
- 3.14 The resubmission proposed continuing treatment criteria based on treatment response. This is assessed after 40 weeks of initial treatment and every 24 weeks thereafter, defined as HbA1c < 7% or a HbA1c reduction  $\geq 2.0\%$  from baseline. These criteria were inconsistent with published guidelines (Australian Diabetes Society Type 2 Diabetes Glycaemic Management Algorithm, June 2024) that recommend individualising glycaemic targets based on patient-centred treatment goals. The ESC considered the continuation criteria were not patient-centred and did not capture the complex clinical needs of many people with type 2 diabetes. The ESC highlighted that the continuation criteria would require patients to discontinue tirzepatide if they have a clinically meaningful reduction HbA1c if their HbA1c remained > 7%. It was also unclear how the treatment response criteria could be practically implemented given the flexible titration approach. The pre-PBAC response proposed the removal of the continuation criteria based on glycaemic response to align with current GLP-1 RA continuing treatment restrictions.
- 3.15 The resubmission requested grandfathering provisions for patients who met the initial treatment criteria before initiating non-PBS-subsidised tirzepatide, prior to the PBS listing date of tirzepatide. The PSCR clarified that patients eligible under the requested grandfathering provisions do not refer to patients on GLP-1 RA without prior SGLT2 inhibitor treatment prior to restriction changes in June 2024. The administrative requirements appeared difficult to implement in practice as they include provision of documentation based on historical points of care as well as recent results demonstrating adequate glycaemic response. The size of the grandfathered

population was unknown but was likely to be hindered by these requirements. The pre-PBAC response stated that with the proposed removal of the continuation criteria based on glycaemia response (see paragraph 3.14), implementation of the grandfathering restriction would only require provision of documented HbA1c results at treatment initiation.

*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 resubmission positioned tirzepatide as an alternative treatment option for patients who meet PBS eligibility criteria for GLP-1 RA treatment for type 2 diabetes and are considered as high risk, defined as either:
  - Patients with BMI  $\geq 35$  kg/m<sup>2</sup>, or
  - Aboriginal and Torres Strait Islander peoples.
- 4.4 Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, 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.
- 4.5 The product information includes special warnings related to gastrointestinal effects (particularly when up titrating the dose in patients with renal impairment). The product information was updated in June 2024 following post marketing safety reports to include additional warnings regarding anaphylactic reaction and angioedema, intestinal obstruction including ileus and dysaesthesia.

- 4.6 The resubmission noted that tirzepatide is subject to ongoing supply constraints due to strong demand for the treatment globally. The TGA currently noted there is limited supply of tirzepatide in Australia and recommends that patients who are unable to obtain the correct strength of tirzepatide should contact their doctor immediately to have their treatment plan assessed. The PSCR stated that the sponsor can ensure sufficient supply to meet the needs of the high-risk type 2 diabetes market. The ESC considered the high demand for tirzepatide in the private market (including as an alternative to semaglutide due to supply shortages) increased the risk of use outside the restriction.

*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 7.4, tirzepatide PSD, July 2023 PBAC meeting).
- 5.2 The resubmission claimed that dulaglutide was not considered as a relevant comparator given more recent PBS utilisation estimates indicate its continuous decline in GLP-1 RA market share. The ESC considered this appeared reasonable.

*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 the points made in the pre-PBAC response the sponsor highlighted that supply has stabilised with the recent approval of the multi-dose pen device with the sponsor was now confident in supply.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (14), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described the effectiveness of tirzepatide in terms of reduction in HbA1c and weight loss. Health care professional input noted that tirzepatide can reduce the likelihood of patients needing insulin therapy with its associated risk of hypoglycaemia. Health care professionals also noted cost as an access issue, with many patients unable to afford tirzepatide privately. One endocrinologist expressed their concern that the necessity for an endocrinologist to be involved would be too exclusive and would reduce access to those most at need. The input from individuals who had used tirzepatide for their own health condition described improvements in blood sugar levels as well as diabetes risk, reductions in food cravings and weight loss. Some individuals noted the gastrointestinal side effects

that they had experienced with treatment, while others reported not experiencing side effects. The comments from individuals also highlighted the lived experience of type 2 diabetes and its impact on quality of life. The input from both individuals who had used tirzepatide for their own health condition and those who would like to use it highlighted cost as a barrier to access.

- 6.3 Comments from National Aboriginal Community Controlled Health Organisation (NACCHO) highlighted the impact of type 2 diabetes on its community, noting that Indigenous adults were 2.9 times as likely to be living with the condition as non-Indigenous adults<sup>1</sup> and are more likely to die from the condition. The PBAC noted diabetes death rates were 4.4 times as high among Indigenous Australians as non-Indigenous Australians.<sup>1</sup> NACCHO also highlighted the significant barriers to access that have been experienced with existing GLP-1 RA medications and stated that having an extra agent in this class would make the supply chain more robust. NACCHO also predicted that any requirement for a patient to be physically reviewed by an endocrinologist would be a significant barrier to care. NACCHO requested consideration to list GLP1 injections and tirzepatide on the PBS for Aboriginal and Torres Strait Islander peoples without the restriction to have a documented HbA1c > 7% (or equivalent BSLs measurement) due to difficulties in pathology testing in some remote areas and to allow treatment for more people who may benefit, including those with pre-diabetes and obesity.
- 6.4 Comments from Diabetes Australia also highlighted the particular challenges faced by Aboriginal and Torres Strait Islander people with diabetes in Australia. Diabetes Australia indicated these challenges include a much higher prevalence than in non-Indigenous Australians, the higher rate of severe-diabetes associated complications, the barriers faced by those in rural/remote areas in accessing endocrinologists and the significant cost barriers for all. In addition, the comments from Diabetes Australia noted the benefits of tirzepatide for those that do not respond well to other GLP-1 RA, and highlighted the mental health stress that can arise for those currently using GLP-1 RAs from not knowing whether they will have ongoing supply.

### ***Clinical trials***

- 6.5 The resubmission was based on the following comparisons previously considered by the PBAC in July 2023:
- Direct comparison of tirzepatide 10 mg and 15 mg versus semaglutide 1.0 mg in patients on background metformin therapy (SURPASS-2).

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<sup>1</sup> Australian Institute of Health and Welfare (AIHW) 2024, *Diabetes: Australian facts*, <https://www.aihw.gov.au/reports/diabetes/diabetes>

- 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.

- 6.6 The resubmission provided a new *post hoc* analyses of the SURPASS-2 trial based on patients with baseline BMI  $\geq 35$  kg/m<sup>2</sup>. A supportive indirect comparison of tirzepatide 5 mg versus semaglutide 0.5 mg using semaglutide 1.0 mg as the common reference was conducted using subgroup data from SURPASS-2 and published subgroup data for patients with baseline BMI  $\geq 35$  kg/m<sup>2</sup> in SUSTAIN-7 (Pratley 2020).
- 6.7 The direct comparison of tirzepatide 5 mg versus semaglutide 1 mg in the SURPASS-2 trial was considered relevant during the evaluation.
- 6.8 There are multiple trials of tirzepatide in the broader SURPASS trial program for type 2 diabetes, including completed trials submitted for regulatory consideration (SURPASS-1, SURPASS-3, SURPASS-4, SURPASS-5, SURPASS-J MONO, SURPASS-J COMBO), a cardiovascular outcomes trial (SURPASS-CVOT, expected completion April 2025), a paediatric study (SURPASS-PEDS, expected completion June 2025) and two GLP-1 RA switching studies (SURPASS-SWITCH and SURPASS-SWITCH2, expected completion July 2024 and completed in October 2023 respectively).
- 6.9 Details of the trials presented in the resubmission are provided in Table 3.

**Table 3: 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
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 <i>post hoc</i> analyses	BMJ Open; 10:e037883

Source: Table 2.2-1, p69 of the resubmission

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

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Tirzepatide versus semaglutide</b>						
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	Post hoc subgroup patient characteristics and treatment effects
<b>Semaglutide versus dulaglutide</b>						
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	Post hoc subgroup treatment effects for semaglutide 0.5 mg

Source: Section 2.4, pp78-96 of the resubmission

Abbreviations: AC, active-control; HbA1c, glycated haemoglobin; MC, multicentre; OL, open-label; R, randomised.

- 6.11 The PBAC considered the risk of bias in the open-label SURPASS-2 and SUSTAIN 7 trials was high (para 7.6, tirzepatide PSD, July 2023 PBAC meeting). The PBAC noted the differential discontinuation between arms in the SURPASS-2 trial, with a higher rate of discontinuations in the tirzepatide 10 mg and 15 mg arms (12-13%) compared to the tirzepatide 5 mg and semaglutide 1 mg arms (8-9%).
- 6.12 The *post hoc* subgroup analyses presented in the resubmission were also associated with a high risk of bias. Treatment discontinuation rates appeared similar between arms in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>, with marginally higher rates of discontinuation in the tirzepatide 10 mg and 15 mg arms (10-11%) compared to the tirzepatide 5 mg and semaglutide 1 mg arms (9%). This was in contrast to the complement group with BMI  $< 35$  kg/m<sup>2</sup> that had higher discontinuation rates in the tirzepatide 10 mg and 15 mg arms (14-15%) compared to the tirzepatide 5 mg and semaglutide 1 mg arms (8-9%).<sup>2</sup> The difference appears to be due to a greater frequency of adverse events leading to treatment discontinuation among patients with BMI  $< 35$  kg/m<sup>2</sup> who received the higher doses of tirzepatide.
- 6.13 Patients included in the clinical trials were required to have inadequate glycaemic control despite treatment with metformin alone. This population may not be representative of patients who had failed treatment with at least one of: metformin, a sulfonylurea or insulin, and had inadequate response/intolerance/contraindication to an SGLT2 inhibitor.

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<sup>2</sup> Note that the results presented in Paragraph 6.12 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.14 The trials used fixed dosing of tirzepatide and semaglutide which was inconsistent with the respective product information documents which recommend flexible titration.
- 6.15 The efficacy and safety of prolonged use of titration doses of tirzepatide (2.5 mg, 7.5 mg, 12.5 mg) is unknown given the use of these doses in the key trial was limited to 4 weeks.
- 6.16 The resubmission claimed the impact of type 2 diabetes is higher among Aboriginal and Torres Strait Islander peoples compared to non-Indigenous people due to their high burden of disease. The resubmission assumed that Aboriginal and Torres Strait Islander peoples would have at least the same capacity to benefit as the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> in the key trial.

### **Comparative effectiveness**

- 6.17 The SURPASS-2 trial assessed two primary estimands to compare efficacy outcomes between treatment groups: the efficacy estimand and the treatment-regimen estimand. The efficacy estimand used data censored for patients who prematurely discontinued treatment or used rescue medication, while the treatment regimen estimand included all in-trial data regardless of discontinuations or use of rescue medication. Both analyses were conducted in patients who underwent randomisation and received at least one dose of the assigned intervention (i.e. modified ITT population).
- 6.18 Results based on the efficacy estimand were numerically higher in favour of tirzepatide versus semaglutide 1 mg, compared to the treatment regimen estimand, as it does not account for the impact of treatment discontinuations, which occurred more frequently in the tirzepatide 10 mg and 15 mg arms compared to the tirzepatide 5 mg and semaglutide 1 mg arms.
- 6.19 Table 5 presents the *post hoc* subgroup analyses of change in HbA1c from baseline to 40 weeks according to baseline BMI category.

Table 5: Change in HbA1c at 40 weeks by baseline BMI  $\geq 35$  kg/m<sup>2</sup> and BMI  $< 35$  kg/m<sup>2</sup>

HbA1c, %	Treatment arm	n	Change from baseline, LSM (SE)	Tirzepatide vs semaglutide, LSM difference (95% CI)	Interaction p-value
<b>Treatment regimen estimand</b>					
ITT	Tirzepatide 5 mg	470	-2.01 (0.04)	<b>-0.15 (-0.28, -0.03)</b>	-
	Tirzepatide 10 mg	469	-2.24 (0.05)	<b>-0.39 (-0.51, -0.26)</b>	
	Tirzepatide 15 mg	469	-2.30 (0.05)	<b>-0.45 (-0.57, -0.32)</b>	
	Semaglutide 1 mg	468	-1.86 (0.05)	-	
BMI $\geq 35$ kg/m <sup>2</sup> <sup>b</sup>	Tirzepatide 5 mg	153	-1.88 <sup>a</sup>	-0.05 (-0.24, 0.15)	NE
	Tirzepatide 10 mg	172	-2.25 <sup>a</sup>	-0.42 (-0.61, -0.23)	
	Tirzepatide 15 mg	172	-2.36 <sup>a</sup>	-0.53 (-0.72, -0.34)	
	Semaglutide 1 mg	158	-1.83 <sup>a</sup>	-	
BMI $< 35$ kg/m <sup>2</sup>	Tirzepatide 5 mg	NE	NE	NE	
	Tirzepatide 10 mg	NE	NE	NE	
	Tirzepatide 15 mg	NE	NE	NE	
	Semaglutide 1 mg	NE	NE	NE	
<b>Efficacy estimand</b>					
ITT	Tirzepatide 5 mg	461	-2.09 (0.05)	<b>-0.23 (-0.36, -0.10)</b>	-
	Tirzepatide 10 mg	459	-2.37 (0.05)	<b>-0.51 (-0.64, -0.38)</b>	
	Tirzepatide 15 mg	464	-2.46 (0.05)	<b>-0.60 (-0.73, -0.47)</b>	
	Semaglutide 1 mg	461	-1.86 (0.05)	-	
BMI $\geq 35$ kg/m <sup>2</sup> <sup>b</sup>	Tirzepatide 5 mg	161	-1.89 (0.08)	-0.10 (-0.32, 0.12)	0.051
	Tirzepatide 10 mg	176	-2.35 (0.08)	-0.57 (-0.78, -0.35)	
	Tirzepatide 15 mg	176	-2.51 (0.08)	-0.73 (-0.94, -0.52)	
	Semaglutide 1 mg	166	-1.78 (0.08)	-	
BMI $< 35$ kg/m <sup>2</sup> <sup>b</sup>	Tirzepatide 5 mg	300	-2.19 (0.06)	-0.30 (-0.47, -0.13)	
	Tirzepatide 10 mg	283	-2.38 (0.06)	-0.49 (-0.67, -0.32)	
	Tirzepatide 15 mg	288	-2.43 (0.06)	-0.54 (-0.71, -0.37)	
	Semaglutide 1 mg	295	-1.89 (0.06)	-	

Source: Table 2.6-11, p137; Table 2.6-12, p139 of the resubmission; Table GPL8.64, p1722 of the SURPASS-2 trial report

Abbreviations: CI, confidence interval; LSM, least squares mean; NE, not estimated; SE, standard error

<sup>a</sup> Standard error was not presented in the trial report.

<sup>b</sup> Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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

6.20 In the whole trial population, treatment with tirzepatide 5 mg, 10 mg and 15 mg was associated with statistically significant reductions in HbA1c from baseline to Week 40 compared with semaglutide 1 mg. The improvements were greater with increasing tirzepatide doses.

6.21 The resubmission claimed the results demonstrated superiority for all three doses of tirzepatide compared to semaglutide 1 mg. The results met the primary outcome of non-inferiority and secondary outcome of superiority in terms of statistical significance; however, only the point estimates for tirzepatide 10 mg and 15 mg based on the efficacy estimand exceed the nominated MCID of 0.5%. The PBAC previously considered that the clinical relevance of change in HbA1c may shift in the context of changing treatment algorithms based on patient-centred outcomes (para 7.10, tirzepatide PSD, July 2023 PBAC meeting).

- 6.22 Pre-specified subgroup analyses of HbA1c results indicated that race and baseline BMI (BMI categories using 27 kg/m<sup>2</sup>, 30 kg/m<sup>2</sup>, 30-35 kg/m<sup>2</sup> and ≥35 kg/m<sup>2</sup> thresholds) may be potential treatment effect modifiers.
- 6.23 *Post hoc* subgroup analyses based on the efficacy estimand also indicated that baseline BMI category (≥35 kg/m<sup>2</sup> and <35 kg/m<sup>2</sup>) was a potential treatment effect modifier for change in HbA1c. Results in both subgroups were in favour of tirzepatide compared to semaglutide 1 mg except for the comparison between tirzepatide 5 mg and semaglutide 1 mg in the subgroup with BMI ≥35 kg/m<sup>2</sup>, which indicated no apparent differences in treatment effect.
- 6.24 Results based on the proportion of patients achieving HbA1c targets of <7.0%, ≤6.5% and <5.7% at Week 40 of the SURPASS-2 trial were previously considered by the PBAC. Treatment with tirzepatide 10 mg or 15 mg weekly was associated with a statistically significant increase in the proportion of patients achieving glycaemic targets compared to semaglutide 1 mg. There were no statistically significant differences between tirzepatide 5 mg and semaglutide 1 mg after adjustment for multiplicity.
- 6.25 *Post hoc* subgroup analyses based on the efficacy estimand indicated that baseline BMI category (≥35 kg/m<sup>2</sup> and <35 kg/m<sup>2</sup>) was not a potential treatment effect modifier in terms of achievement of HbA1c targets. The results were generally consistent with the whole trial population that favoured the higher doses of tirzepatide, with no apparent differences for the comparison between tirzepatide 5 mg compared to semaglutide 1 mg.
- 6.26 The PBAC previously considered results of Bucher method indirect comparisons of tirzepatide 5 mg (based on the SURPASS-2 trial) versus semaglutide 0.5 mg (based on the SUSTAIN-7 trial) using semaglutide 1 mg as a common reference for change in HbA1c (%). In the whole trial population, treatment with tirzepatide 5 mg was associated with a statistically significant reduction in HbA1c compared to semaglutide 0.5 mg. The point estimate exceeded the nominated MCID of 0.5%. The point estimate also favoured tirzepatide 5 mg compared to semaglutide 0.5 mg in the *post hoc* subgroup with BMI ≥35 kg/m<sup>2</sup>, but the result did not achieve statistical significance or exceed the nominated MCID.
- 6.27 Table 6 presents *post hoc* subgroup analyses of change in body weight (kg) at 40 weeks according to baseline BMI category ≥35 kg/m<sup>2</sup> and <35 kg/m<sup>2</sup>.

Table 6: Change in body weight (kg) at 40 weeks by baseline BMI  $\geq 35$  kg/m<sup>2</sup> and BMI  $< 35$  kg/m<sup>2</sup>

Body weight, kg	Treatment arm	n	Change from baseline, LSM (SE)	Tirzepatide vs semaglutide, LSM difference (95% CI)	Interaction p-value
<b>Treatment regimen estimand</b>					
ITT	Tirzepatide 5 mg	470	-7.6 (0.33)	<b>-1.9 (-2.8, -1.0)</b>	-
	Tirzepatide 10 mg	469	-9.3 (0.32)	<b>-3.6 (-4.5, -2.7)</b>	
	Tirzepatide 15 mg	469	-11.2 (0.32)	<b>-5.5 (-6.4, -4.6)</b>	
	Semaglutide 1 mg	468	-5.7 (0.32)	-	
BMI $\geq 35$ kg/m <sup>2</sup> <sup>a</sup>	Tirzepatide 5 mg	153	-9.04	-2.6 (-4.4, -0.8)	NE
	Tirzepatide 10 mg	171	-11.32	-4.9 (-6.6, -3.1)	
	Tirzepatide 15 mg	172	-14.09	-7.6 (-9.4, -5.9)	
	Semaglutide 1 mg	159	-6.46	-	
BMI $< 35$ kg/m <sup>2</sup>	Tirzepatide 5 mg	NE	NE	NE	
	Tirzepatide 10 mg	NE	NE	NE	
	Tirzepatide 15 mg	NE	NE	NE	
	Semaglutide 1 mg	NE	NE	NE	
<b>Efficacy estimand</b>					
ITT	Tirzepatide 5 mg	461	-7.8 (0.33)	<b>-1.7 (-2.6, -0.7)</b>	-
	Tirzepatide 10 mg	459	-10.3 (0.34)	<b>-4.1 (-5.0, -3.2)</b>	
	Tirzepatide 15 mg	464	-12.4 (0.34)	<b>-6.2 (-7.1, -5.3)</b>	
	Semaglutide 1 mg	462	-6.2 (0.33)	-	
BMI $\geq 35$ kg/m <sup>2</sup> <sup>a</sup>	Tirzepatide 5 mg	161	-9.3 (0.66)	-2.3 (-4.2, -0.5)	<b>&lt;0.001</b>
	Tirzepatide 10 mg	176	-12.2 (0.63)	-5.3 (-7.0, -3.5)	
	Tirzepatide 15 mg	176	-15.5 (0.63)	-8.6 (-10.3, -6.8)	
	Semaglutide 1 mg	166	-6.9 (0.65)	-	
BMI $< 35$ kg/m <sup>2</sup> <sup>a</sup>	Tirzepatide 5 mg	308	-7.1 (0.35)	-1.3 (-2.3, -0.4)	
	Tirzepatide 10 mg	288	-9.0 (0.36)	-3.3 (-4.3, -2.3)	
	Tirzepatide 15 mg	291	-10.4 (0.36)	-4.6 (-5.6, -3.7)	
	Semaglutide 1 mg	301	-5.7 (0.35)	-	

Source: Table 2.5-3, p103; Table 2.6-14, p143; p56, Attachment A2.15 of the resubmission; Table GPL8.89, p2203 of the SURPASS-2 trial report

Abbreviations: CI, confidence interval; LSM, least squares mean; NE, not estimated; SE, standard error

<sup>a</sup> Note that the results presented in Table 6 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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

6.28 In the whole trial population, treatment with tirzepatide 5 mg, 10 mg and 15 mg was associated with statistically significant reductions in body weight at Week 40. The magnitude of effect increased with increasing tirzepatide dose.

6.29 Pre-specified subgroup analyses of body weight results indicated that age, baseline BMI (BMI categories using 30 kg/m<sup>2</sup>, 30-35 kg/m<sup>2</sup> and  $\geq 35$  kg/m<sup>2</sup> thresholds), duration of diabetes, geographic region and ethnicity may be potential treatment effect modifiers.

6.30 *Post hoc* subgroup analyses based on the efficacy estimand also indicated that baseline BMI category ( $\geq 35$  kg/m<sup>2</sup> and  $< 35$  kg/m<sup>2</sup>) was a potential treatment effect modifier for change in body weight. Results in both subgroups were in favour of tirzepatide, with greater improvements observed in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> which may be due to higher baseline mean body weight.

- 6.31 Results based on the proportion of patients achieving weight loss targets of  $\geq 5\%$ ,  $\geq 10\%$  and  $\geq 10\%$  were previously considered by the PBAC. Treatment with tirzepatide 5 mg, 10 mg and 15 mg weekly were all associated with a numerical increase in the proportion of patients achieving weight loss targets compared to semaglutide 1 mg (unadjusted for multiplicity).
- 6.32 The resubmission claimed that weight loss of 5% to 10% is clinically important and likely to provide both glycaemic and non-glycaemic benefits (e.g. blood pressure, lipids), and that intensive weight management with target weight loss of  $\geq 10\%$  is recommended in Australian guidelines (Australian Diabetes Society 2022). In July 2023, the PBAC reaffirmed previously raised concerns regarding the lack of long-term data supporting reductions in downstream complications for treatments claiming weight loss benefits (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). The ESC noted there was limited evidence on cardiovascular outcomes for people with type 2 diabetes using GLP-1 RAs. The PSCR provided results from a retrospective cohort study in the US based on individuals with type 2 diabetes initiating tirzepatide or GLP-1 RA between June 2022 and June 2023 (Chuang 2024<sup>3</sup>). The PSCR noted that tirzepatide was associated with a lower risk of all-cause mortality (adjusted hazard ratio 0.58; 95% CI: 0.45, 0.75) and major adverse cardiovascular events (adjusted hazard ratio 0.80; 95% CI: 0.71, 0.91) compared to GLP-1 RAs. The ESC considered the validity of these results was uncertain as the study was not included in the resubmission and therefore was not evaluated.
- 6.33 *Post hoc* subgroup analyses based on the efficacy estimand indicated that baseline BMI category ( $\geq 35$  kg/m<sup>2</sup> and  $< 35$  kg/m<sup>2</sup>) was not a potential treatment effect modifier in terms of achievement of weight loss targets. Results in both subgroups were consistent with results in the whole trial population that favoured tirzepatide compared to semaglutide 1 mg, with greater proportions of patients achieving the weight loss target when using increasing doses of tirzepatide.
- 6.34 The PBAC previously considered results of a Bucher method indirect comparison of tirzepatide 5 mg (based on the SURPASS-2 trial) versus semaglutide 0.5 mg (based on the SUSTAIN-7 trial) using semaglutide 1 mg as a common reference for change in body weight (kg). Treatment with tirzepatide 5 mg was associated with a statistically significant reduction in mean body weight compared to semaglutide 0.5 mg. Results in the *post hoc* subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> were consistent, with a numerically greater reduction in body weight based on the point estimate.
- 6.35 Additional analyses were conducted for changes in lipid parameters (HDL, LDL), vital signs (heart rate, systolic blood pressure) and estimated glomerular filtration rate for

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<sup>3</sup> Chuang, M. H., J. Y. Chen, H. Y. Wang, Z. H. Jiang, and V. C. Wu. 2024. "Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes." *JAMA Netw Open* 7 (8):e2427258.

the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>, used to inform the economic analysis. The results were consistent with primary analyses in the ITT population that indicated no apparent differences in these measures between tirzepatide and semaglutide 1 mg.

- 6.36 The PBAC previously considered results based on quality of life measures in the SURPASS-2 whole trial population. There were no apparent differences between all doses of tirzepatide and semaglutide in terms of generic quality of life outcomes (EQ-5D VAS and EQ-5D-5L). Treatment with tirzepatide 15 mg was associated with a relatively small improvement in IWQOL-Lite-CT scores (total score, physical and psychosocial composite subscores) compared to semaglutide 1 mg. There were no apparent differences between tirzepatide 5 mg and 10 mg compared with semaglutide in terms of the IWQOL-Lite-CT total score and psychosocial composite score, with relatively small improvements in the IWQOL-Lite-CT physical composite subscore. Results based on quality of life measures in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> were broadly consistent with results in the whole trial population.

### **Comparative harms**

- 6.37 Table 7 presents an overall summary of adverse events reported with tirzepatide and semaglutide in the SURPASS-2 trial, including a *post hoc* analysis of adverse events in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>.

Table 7: Summary of key adverse events in the SURPASS-2 trial

Patients, n (%)	ITT				BMI ≥35 kg/m <sup>2</sup> <sup>a</sup>			
	TZP 5 mg N=470	TZP 10 mg N=469	TZP 15 mg N=470	SEMA 1 mg N=469	TZP 5 mg N=162	TZP 10 mg N=181	TZP 15 mg N=179	SEMA 1 mg N=168
Any AE	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)	112 (69.1)	126 (69.6)	127 (70.9)	114 (67.9)
Treatment-related AE	188 (40.0)	221 (47.1)	225 (47.9)	194 (41.4)	64 (39.5)	88 (48.6)	88 (49.2)	71 (42.3)
Serious AE	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)	13 (8.0)	14 (7.7)	12 (6.7)	4 (2.4)
AE leading to treatment discontinuation	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)	11 (6.8)	13 (7.2)	11 (6.1)	7 (4.2)
AE leading to study discontinuation	5 (1.1)	8 (1.7)	5 (1.1)	4 (0.9)	4 (2.5)	4 (2.2)	1 (0.6)	2 (1.2)
Deaths	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)	3 (1.9)	2 (1.1)	1 (0.6)	1 (0.6)
<b>Adverse events of special interest</b>								
Gastrointestinal events	188 (40.0)	216 (46.1)	211 (44.9)	193 (41.2)	NE	NE	NE	NE
Hypoglycaemia	3 (0.6)	1 (0.2)	8 (1.7)	2 (0.4)	1 (0.6)	0 (0.0)	5 (2.8)	1 (0.6)
Severe hypoglycaemia	1 (0.2)	0	1 (0.2)	0	NE	NE	NE	NE
Injection site reaction	9 (1.9)	13 (2.8)	21 (4.5)	1 (0.2)	NE	NE	NE	NE
Adjudicated pancreatitis	0	2 (0.4)	2 (0.4)	3 (0.6)	NE	NE	NE	NE
Cholelithiasis	4 (0.9)	4 (0.9)	4 (0.9)	2 (0.4)	NE	NE	NE	NE
Hypersensitivity	9 (1.9)	13 (2.8)	8 (1.7)	11 (2.3)	NE	NE	NE	NE
Diabetic retinopathy	0	2 (0.4)	0	0	NE	NE	NE	NE

Source: Table 2.5-1, p110; Table 2.6-17, p149; Table 2.6-18, p152 of the resubmission; Table 2, Frias 2021 publication; Table GPL5.27, SURPASS-2 trial report

Abbreviations: AE, adverse event; NE, not estimated; SEMA, semaglutide; TZP, tirzepatide

Note: Hypoglycaemia events were defined as blood glucose level <3 mmol/L or severe hypoglycaemia

<sup>a</sup> Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.38 Treatment with tirzepatide (all dose strengths) was associated with a higher incidence of serious adverse events compared to semaglutide. The difference was primarily driven by an increase in cardiac and gastrointestinal disorders with tirzepatide treatment.
- 6.39 The most frequently reported class of adverse events was gastrointestinal disorders including nausea, diarrhoea, vomiting, dyspepsia, decreased appetite, constipation and abdominal pain. The incidence of gastrointestinal disorders was similar between the tirzepatide 5 mg and semaglutide arms, with higher incidence reported in the tirzepatide 10 mg and 15 mg arms. The difference was primarily driven by an increased incidence of diarrhoea with the higher dose strengths of tirzepatide. The majority of gastrointestinal adverse events were of mild to moderate severity. The prevalence of gastrointestinal events peaked within the dose escalation period for each treatment and then started to decline over time.

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- 6.40 There was a small number of clinically significant hypoglycaemia events (blood glucose <3.0 mmol/L or severe hypoglycaemia) in the trial, with a higher incidence in the tirzepatide 15 mg arm and similar incidence between tirzepatide 5 mg, tirzepatide 10 mg and semaglutide arms.
- 6.41 Results based on the subgroup analysis appeared similar to the whole trial population, with similar incidence of adverse events between the tirzepatide 5 mg and semaglutide 1 mg arms and higher incidence in the tirzepatide 10 mg and 15 mg arms.
- 6.42 The impact of baseline BMI category on adverse events of special interest (apart from clinically significant hypoglycaemia) was unknown as the data were not presented in the resubmission.
- 6.43 The resubmission stated that indirect comparisons of safety between the SURPASS-2 and SUSTAIN 7 trials were unreliable due to substantial differences in the reported incidence of events in the common comparator arm.
- 6.44 The resubmission provided additional data on potential safety concerns with tirzepatide based on a Periodic Safety Update Report (May 2023 to November 2023). The report includes the use of tirzepatide for type 2 diabetes, obesity/overweight (with or without diabetes), obstructive sleep apnoea, non-alcoholic steatohepatitis, heart failure with preserved ejection fraction and chronic kidney disease.
- 6.45 There were no important identified risks in the risk management plan. Important potential risks include medullary thyroid cancer, pancreatic malignancy and diabetic retinopathy complications. Missing information includes use in pregnancy and lactation.
- 6.46 New safety signals were identified during the reporting period, including aspiration while undergoing general anaesthesia and deep sedation, dysgeusia (taste disorder), suicidal ideation and alopecia/hair loss. The reference safety information was updated to include warnings related to pulmonary aspiration in patients undergoing general anaesthesia or deep sedation, and dysgeusia was included as an adverse drug reaction. Suicidal ideation and alopecia/hair loss safety signals were refuted by the sponsor following a review of the available data. The evaluation of these signals was closed during the reporting period.
- 6.47 Late-breaking safety signals were identified during the reporting period, including malnutrition and cachexia (wasting syndrome), intestinal obstruction and ileus (inability of intestine to contract normally) and gastroparesis (delayed gastric emptying). Malnutrition and cachexia and gastroparesis signals were considered as potential risks and were included under special warnings and precautions in the reference safety information. The intestinal obstruction and ileus signal was refuted by the sponsor. The evaluation of these signals is ongoing.
- 6.48 The Periodic Safety Update Report stated that global labelling changes to reflect the updated reference safety information are ongoing.

- 6.49 The ESC noted that an observational study<sup>4</sup> suggested an association between semaglutide use and nonarteritic anterior ischemic optic neuropathy.
- 6.50 The ESC advised that safety signals for GLP-1 RAs were still emerging as there is limited longer term safety data.

### Benefits/harms

- 6.51 A benefits/harms table for tirzepatide 5 mg versus 1 mg was not presented given the data did not support superior efficacy.
- 6.52 A summary of comparative benefits and harms for tirzepatide versus semaglutide based on the SURPASS-2 trial population is presented in Table 8.

**Table 8: Comparative benefits and harms for tirzepatide versus semaglutide 1 mg in patients (treatment regimen estimand)**

	Tirzepatide	Semaglutide	Treatment difference
<b>Tirzepatide 10 mg versus semaglutide 1 mg</b>			
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%
<b>Tirzepatide 15 mg versus semaglutide 1 mg</b>			
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, p101; Table 2.5-4, p106 and Table 2.5-1, p110 of the resubmission

- 6.53 Based on the SURPASS-2 trial, for every 100 patients with type 2 diabetes 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.

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<sup>4</sup> Hathaway, Jimena Tatiana et al. "Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide." *JAMA ophthalmology* vol. 142,8 (2024): 732-739.

- 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 5 additional patients with any adverse event, 3 additional patients with serious adverse events and 4 additional patients with adverse events leading to treatment discontinuation.
- 6.54 Based on the SURPASS-2 trial, for every 100 patients with type 2 diabetes 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  $\geq 5\%$  weight loss, 33 additional patients would experience  $\geq 10\%$  weight loss and 28 additional patients would experience  $\geq 15\%$  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 5 additional patients with any adverse event, 3 additional patients with serious adverse events and 4 additional patients with adverse events leading to treatment discontinuation.
- 6.55 There were no apparent differences in treatment effect in terms of achievement of glycaemic and weight loss targets, safety outcomes and generic and disease-specific quality of life measures between the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> and the whole trial population in SURPASS-2.

### ***Clinical claim***

- 6.56 The resubmission described tirzepatide 5 mg once weekly as superior in terms of efficacy compared to semaglutide 0.5 mg once weekly. The PBAC previously considered the claim was reasonable based on an indirect comparison of the broader SURPASS-2 and SUSTAIN 7 trial populations (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). However, it was unclear whether the superiority claim was adequately supported in the target subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>.
- 6.57 The resubmission described tirzepatide 5 mg once weekly as non-inferior in terms of safety compared to semaglutide 0.5 mg once weekly. The PBAC previously considered that the claim was inadequately supported by the data (para 6.57, tirzepatide PSD, July 2023 PBAC meeting). The safety analysis for the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> was also based on an indirect comparison of SURPASS-2 and SUSTAIN 7, which was limited by differences in the incidence of events in the common reference arm.
- 6.58 The resubmission did not make a clinical claim of efficacy or safety for tirzepatide 5 mg once weekly versus semaglutide 1 mg once weekly. The PBAC previously considered that the 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). Subgroup data in those with BMI  $\geq 35$  kg/m<sup>2</sup> were consistent with data in the whole trial population.

- 6.59 The resubmission described tirzepatide 10 mg or 15 mg once weekly as superior in terms of efficacy compared to semaglutide 1 mg once weekly. The PBAC previously considered the claim was reasonable (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). Results in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> appeared consistent with results in the whole trial population.
- 6.60 The resubmission described tirzepatide 10 mg or 15 mg once weekly as non-inferior in terms of safety compared to semaglutide 1 mg once weekly. The PBAC previously considered the claim was inadequately supported (para 7.11, tirzepatide PSD, July 2023 PBAC meeting). Safety data in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> appeared similar to the whole trial population.
- 6.61 The following issues should be considered:
- There were multiple evidence gaps in the clinical data presented:
    - No data for tirzepatide administered using a flexible titration approach, particularly the use of titration doses (2.5 mg, 7.5 mg and 12.5 mg) beyond 4 weeks in the trial.
    - No data for switching from other combinations of type 2 diabetes medications (including with insulin) to dual therapy with metformin only.
    - No data on longer term effects of tirzepatide on diabetes-related complications including cardiovascular outcomes. The PSCR provided results from a retrospective cohort study in the US based on individuals with type 2 diabetes initiating tirzepatide or GLP-1 RA between June 2022 and June 2023 (Chuang 2024<sup>5</sup>). The PSCR noted that tirzepatide was associated with a lower risk of all-cause mortality (adjusted hazard ratio 0.58; 95% CI: 0.45, 0.75) and major adverse cardiovascular events (adjusted hazard ratio 0.80; 95% CI: 0.71, 0.91) compared to GLP-1 RAs. The ESC considered the validity of these results was uncertain as the study was not included in the resubmission and therefore was not evaluated.
  - The long-term safety profile of tirzepatide was uncertain, with updates to global reference safety information in response to emerging safety signals including pulmonary aspiration under anaesthesia, dysgeusia, malnutrition and cachexia, and gastroparesis.

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<sup>5</sup> Chuang, M. H., J. Y. Chen, H. Y. Wang, Z. H. Jiang, and V. C. Wu. 2024. "Clinical Outcomes of Tirzepatide or GLP-1 Receptor Agonists in Individuals With Type 2 Diabetes." *JAMA Netw Open* 7 (8):e2427258.

- 6.62 The PBAC reaffirmed its July 2023 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. The PBAC considered results for 10 mg and 15 mg tirzepatide in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> appeared consistent with results in the whole trial population. The PBAC considered the claim of superior comparative efficacy for tirzepatide 5 mg once weekly compared to semaglutide 0.5 mg once weekly in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> was uncertain but likely reasonable.
- 6.63 The PBAC also reaffirmed its July 2023 advice that the comparison of tirzepatide 5 mg and semaglutide 1 mg remained relevant, and noted that this comparison did not support a clinically meaningful difference in either the whole trial population or the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>.
- 6.64 The PBAC reaffirmed its July 2023 advice that the claim of non-inferior comparative safety was not adequately supported by the data for any of the comparisons.

### ***Economic analysis***

- 6.65 The resubmission presented a modelled economic evaluation of tirzepatide 15 mg weekly compared to semaglutide 1 mg weekly, based on clinical data from the SURPASS-2 trial post hoc subgroup with baseline BMI  $\geq 35$  kg/m<sup>2</sup>, with additional modelled data. Scenario analyses were also presented for comparisons of tirzepatide 10 mg versus semaglutide 1 mg and tirzepatide 5 mg versus semaglutide 0.5 mg.
- 6.66 The resubmission claimed that the comparison of tirzepatide 5 mg versus semaglutide 1 mg was not relevant, as the majority of patients would use tirzepatide 5 mg as a temporary dose only before titrating to higher dose. The PBAC previously found this comparison relevant given that 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 7.7, 7.11 tirzepatide PSD, July 2023 PBAC meeting). Therefore, a comparison of tirzepatide 5 mg weekly with semaglutide 1 mg weekly was presented during the evaluation.
- 6.67 The main changes to the economic evaluation in the current resubmission compared with the July 2023 submission include:
- Model baseline characteristics and treatment effects in the current submission were based on the post hoc baseline BMI  $\geq 35$  kg/m<sup>2</sup> subgroup of the SURPASS-2 trial; compared to the whole trial population in the July 2023 submission. The ESC noted that this was appropriate, although considered that some issues remain around representativeness of the population.
  - Tiered pricing for tirzepatide was incorporated in the current submission (effective DPMQ \$ [REDACTED] for 5 mg, \$ [REDACTED] for 10 mg, and \$ [REDACTED] for 15 mg); compared to flat pricing in the July 2023 submission (effective DPMQ \$ [REDACTED] for 5 mg, 10 mg, 15 mg).

- The HbA1c threshold for insulin initiation and intensification was lowered from 7.5% to 7.0%. The ESC considered use of a 7.0% threshold was not adequately justified and noted this was not as previously advised by the PBAC, which suggested an 8.0% threshold.
- The disutility associated with each hypoglycaemia event was reduced from 0.005 to 0.003. The ESC considered this was appropriate.
- Biomarker drift, previously only included for HbA1c, was included for all biomarkers, except for BMI, systolic blood pressure, and heart rate. The ESC noted the inclusion of biomarker drift for non-statistically significant differences was selective and not well supported, and considered the model should include all biomarker drift.
- The resubmission also corrected errors in the previous model’s inconsistent application of eGFR treatment effects across treatment arms, insulin dosing per script, and use of the wrong source of mortality for patients with a history of events but no events; and updated unit costs, the inflation factor for diabetes complication costs, and the source of Australian life tables. The ESC considered these changes to be generally appropriate.

6.68 Table 9 summarises the key components of the economic evaluation.

**Table 9: 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)
Methods used to generate results	Patient-level microsimulation model (10,000 patients; runtime approximately 30-40 minutes).
Treatments	Tirzepatide 15 mg weekly or semaglutide 1 mg weekly in combination with metformin; with 2 further lines of insulin intensification therapy (basal insulin, basal and bolus insulin).
Model structure	<p>The model tracks individual patient-level changes in surrogate biomarkers over time.</p> <p>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.</p> <p>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).</p>
Patient characteristics and circumstances of use	<p>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 trial <i>post hoc</i> subgroup with BMI <math>\geq 35</math> kg/m<sup>2</sup> (compared to the whole trial population in the July 2023 submission).</p> <p>The resubmission sampled the baseline characteristics of modelled patients assuming a normal distribution around mean values.</p> <p>The modelled circumstances of use assumed flat dosing of GLP-1 RA/GIP therapies, assumed that patients would not prematurely discontinue therapy, assumed patients would switch to insulin when</p>

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Component	Description
	<p>HbA1c &gt;7.0% and would intensify treatment if the same threshold was reached again (compared to HbA1c &gt;7.5% in the July 2023 submission), assumed GLP-1 RA/GIP therapy must be stopped with the initiation of insulin, and assumed flat dosing of insulin therapies.</p>
Transition probabilities	<p>Treatment effects (on HbA1c, systolic blood pressure, LDL cholesterol, HDL cholesterol, BMI, eGFR and heart rate) for GLP-1 RA/GIP therapy were based on the SURPASS-2 trial <i>post hoc</i> subgroup with BMI <math>\geq 35</math> kg/m<sup>2</sup> (compared to the whole trial population in the July 2023 submission). 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 (the July 2023 submission assumed UKPDS progression of HbA1c only). No modelled patients were allowed to discontinue prematurely.</p> <p>Patients were assumed to intensify therapy with insulin when HbA1c was &gt;7.0% (compared to &gt;7.5% in the July 2023 submission). HbA1c levels were assumed to remain unaffected by patients discontinuing GLP-1 RA/GIP therapy when initiating insulin therapy. Insulin intensification was assumed to revert BMI, systolic blood pressure and heart rate to baseline values, with no impact on LDL cholesterol, HDL cholesterol, and eGFR (compared to all biomarkers except HbA1c reverting to baseline in the July 2023 submission). Insulin treatment effects on HbA1c were estimated based on a systematic review of insulin studies (Willis 2017). Biomarker progression on insulin was the same as for GLP-1 RA/GIP therapies. No modelled patients were allowed to discontinue prematurely.</p> <p>Adverse event risk for GLP-1 RA/GIP therapy was estimated based on the SURPASS-2 trial <i>post hoc</i> subgroup with baseline BMI <math>\geq 35</math> kg/m<sup>2</sup> (compared to the whole trial population in the July 2023 submission). Adverse event risk for insulin was estimated based on the ReFLECT observational study (Fadini 2019).</p> <p>The risk of diabetes complications was based on the UKPDS OM2 risk equations.</p> <p>The risk of death was based on UKPDS OM2 risk equations for 'first year of events' and 'subsequent years of events'; and Australian life tables for 'years with no event history or events' and 'years with history of events but no events'.</p>
Utility values	<p>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).</p> <p>The disutility values for ulcer and renal failure were estimated based on the CODE-2 study (Bagust and Beale, 2005).</p> <p>Age based disutility values were estimated based on an Australian general population sample (Clemens 2014); and assumed to apply to all modelled patients 55 years or older (compared to patients 58 years or older in the July 2023 submission).</p> <p>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.</p> <p>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 &gt;25 kg/m<sup>2</sup>.</p>
Costs	<p>The cost of tirzepatide was based on fixed dosing at 5, 10 or 15 mg per week; and the proposed tiered effective DPMQs \$█, \$█, \$█ (compared to flat pricing at \$█ in the July 2023 submission). The cost of semaglutide was based on fixed dosing of 1 mg per week and the effective DPMQ of \$█ (as this was known to the sponsor). The costs of metformin, insulin glargine and insulin aspart were based on WHO defined daily doses and published DPMQs (no special pricing arrangements apply).</p> <p>The resubmission assumed that there were no additional costs associated with the management of nausea or hypoglycaemia.</p> <p>The resubmission estimated the cost of insulin administration based on the advertised price of consumables (blood glucose testing strips, injection needles and lancets) from the Diabetes Shop website (<a href="https://diabetesshop.com">https://diabetesshop.com</a>). 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.</p>

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<b>Component</b>	<b>Description</b>
	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 (inflation factor 3.750) compared to the CPI Health index in the July 2023 submission (inflation factor 2.705).
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1-2, pp208-209 of the resubmission.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic peptide; GLP-1 RA glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; UKPDS (OM2), United Kingdom Prospective Diabetes Study (Outcomes Model 2); WBC, white blood cell.

- 6.69 In the model, a set of baseline characteristics (demographics, biomarkers, history of complications) was individually generated for each modelled patient. Over the course of the model, patients experience changes in biomarkers due to modelled treatment effects for each therapy, and assumptions regarding disease progression.
  
- 6.70 Patients are initially treated with GLP-1 RA/GIP therapies until their HbA1c levels increase to 7.0% after which they discontinue GLP-1 RA/GIP therapy and switch to basal insulin. Patients are then assumed to remain on fixed dose insulin glargine until their HbA1c levels again increase to 7.0% after which they switch to an insulin intensification regimen (basal with bolus insulin). While receiving treatment, patients are at risk of experiencing nausea (GLP-1 RA/GIP therapies for the first year only) and hypoglycaemia episodes.
  
- 6.71 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.
  
- 6.72 In the model, treatment effects are applied for the first year of treatment; after which outcomes may remain constant or progress over time while remaining on treatment. Table 10 presents the modelled treatment effects for tirzepatide and semaglutide. ESC highlighted that the treatment effects for LDL cholesterol, heart rate and hypoglycaemia rate did not have the expected dose response pattern, such as tirzepatide 5 mg having a numerically higher hypoglycaemia rate than tirzepatide 10 mg. The ESC considered this could be due to small patient numbers. The ESC considered this inconsistency could be addressed by smoothing the data across tirzepatide doses.

Table 10: Modelled treatment effects

Component	Tirzepatide 15 mg	Tirzepatide 10 mg	Tirzepatide 5 mg	Semaglutide 1 mg
<b>First-line treatments (based on the SURPASS-2 trial post hoc subgroup with BMI <math>\geq</math>35 kg/m<sup>2</sup>)<sup>c</sup></b>				
HbA1c, mean % (SD)	-2.51 (0.94)	-2.35 (0.95)	-1.89 (0.94)	-1.78 (0.95)
SBP, mean mmHg (SD)	-5.70 (12.07)	-5.60 (12.07)	-4.70 (12.12)	-3.40 (12.02)
LDL cholesterol, mean mmol/L (SD)	-0.07 (0.66)	-0.06 (0.66)	-0.20 (0.63)	-0.10 (0.66)
HDL cholesterol, mean mmol/L (SD)	+0.07 (0.18)	+0.07 (0.18)	+0.05 (0.17)	+0.04 (0.17)
BMI, mean kg/m <sup>2</sup> (SD)	-5.70 (3.01)	-4.50 (3.02)	-3.40 (2.98)	-2.60 (2.94)
eGFR, mean mL/min/1.73m <sup>2</sup> (SD)	-5.90 (9.71)	-5.00 (9.65)	-4.60 (9.62)	-4.50 (9.71)
Heart rate, mean bpm (SD)	+2.50 (8.000)	+2.10 (8.00)	+2.60 (8.04)	+1.70 (7.97)
WBC, mean (SD)	0.00	0.00	0.00	0.00
Haemoglobin, mean (SD)	0.00	0.00	0.00	0.00
Hypoglycaemia rate, mean per 100 patient years (SD) <sup>a</sup>	3.09	0.00	0.68	0.65
Proportion with nausea in first year <sup>b</sup>	39/179 (21.8%)	36/181 (19.9%)	25/162 (15.4%)	33/168 (19.6%)

Source: Table 3.4-2, p226 of the resubmission with additional data extracted during the evaluation based on 'A8.1\_Tirzepatide Section 3 Model' spreadsheet provided with the resubmission

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell count

<sup>a</sup> Based on the reported event rates for clinically significant hypoglycaemia (severe event requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose  $<$ 3.0 mmol/L) in the SURPASS-2 *post hoc* subgroup with BMI  $\geq$ 35 kg/m<sup>2</sup>.

<sup>b</sup> Based on the proportion of patients with nausea of any severity in the SURPASS-2 *post hoc* subgroup with BMI  $\geq$ 35 kg/m<sup>2</sup>; assumed to apply in the first year of treatment only.

<sup>c</sup> Note that the results presented in Table 10 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.73 It was unclear whether the modelled patient characteristics, based on the SURPASS-2 *post hoc* subgroup with BMI  $\geq$ 35 kg/m<sup>2</sup>, would be representative of the proposed Australian population (patients who have previously failed SGLT2 inhibitor therapies due to inadequate response, intolerance or contraindication). A comparison between the SURPASS-2 subgroup and data from an Australian study (Thakur 2021) for patients with BMI  $\geq$ 35 kg/m<sup>2</sup> identified substantial differences in treatments used for type 2 diabetes. The SURPASS-2 trial selected patients treated with background metformin only while patients in Thakur 2021 received a broad range of treatments including metformin (91%), insulin (62%), sulfonylurea (31%), SGLT2 inhibitor (25%), DPP4 inhibitor (23%) and GLP-1 RA (13%). The comparison also indicated that Australian patients had a higher mean HbA1c level, and greater proportions of patients with a history of cardiovascular disease (ischaemic heart disease, stroke), chronic kidney disease and other complications (peripheral neuropathy, lower limb amputation) compared to the SURPASS-2 trial subgroup.

6.74 The economic model assumes flat dosing of both tirzepatide (5 mg, 10 mg, 15 mg weekly) and semaglutide (1 mg weekly); which, while consistent with the trial data, is unlikely to reflect use in clinical practice as the product information documents for both treatments recommend flexible dose titration. The model also assumes that patients cannot prematurely discontinue therapy; which is inconsistent with the SURPASS-2 *post hoc* subgroup data that indicated 9.3% of tirzepatide 5 mg, 9.9% of tirzepatide 10 mg, 10.6% of tirzepatide 15 mg and 8.9% of semaglutide 1 mg patients

discontinued therapy over the 40 week trial duration.<sup>6</sup> The PBAC previously considered that the assumptions regarding modelled circumstances of use (including fixed dosing of GLP-1 RA/GIP and insulin therapies, and perfect persistence), were unlikely to reflect Australian clinical practice (para 7.13, tirzepatide PSD, July 2023 PBAC meeting).

- 6.75 The July 2023 model assumed no progression over time for all biomarkers except HbA1c, which the PBAC considered was not clinically appropriate and favoured tirzepatide; and specified that a revised base case should incorporate UKPDS drift for all biomarkers (para 7.14, 7.16, tirzepatide PSD, July 2023 PBAC meeting). In the revised model, GLP-1 RA/GIP biomarker treatment effects are applied for the first year of treatment based on the SURPASS-2 *post hoc* subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>; after which BMI, systolic blood pressure, heart rate remain constant (based on evidence from GLP-1 RA cardiovascular outcomes trials), while HbA1c, HDL cholesterol, LDL cholesterol, eGFR, white blood cell count, and haemoglobin progress over time (based on UKPDS OM2 risk equations), prior to initiating insulin therapy when a patient's HbA1c reaches 7%. Insulin treatment effects for HbA1c are based on the results of a systematic review (Willis 2007); with treatment effects for other biomarkers dependent on assumptions regarding biomarker progression with GLP-1 RA/GIP therapy (reversion to baseline values for biomarkers that remain constant; no treatment effect for biomarkers with UKPDS progression). Subsequent biomarker progression on insulin therapy is the same as for first-line treatment (constant for BMI, systolic blood pressure, and heart rate; progression over time for other biomarkers). The interdependency between treatment effects and biomarker progression in the model was inadequately justified and resulted in implausible scenarios such as systolic blood pressure being fixed at 2 different levels with GLP-1 RA/GIP treatment and insulin treatment. Similarly, a patient's BMI is fixed at 3 different levels associated with GLP-1 RA/GIP treatment, insulin initiation, and subsequent insulin intensification. The ESC noted more recent data from GLP-1 RA cardiovascular outcomes trials suggests smaller HbA1c drift than modelled in the resubmission which reduced the ICER.
- 6.76 Key drivers of the economic model are summarised in Table 11.

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<sup>6</sup> Note that the results presented in Table 10 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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Table 11: Key drivers of the model

Description	Method/Value	Impact
Tirzepatide continuation criteria	The economic model did not appropriately incorporate the proposed tirzepatide continuation criteria, requiring patients to achieve HbA1c <7% OR a HbA1c reduction from baseline is ≥2%. The model assumes patients will continue tirzepatide until their HbA1c exceeds 7%. The same threshold was used for semaglutide, which does not have any continuation criteria.	High, favours tirzepatide
Insulin initiation and intensification threshold	In the model, patients switch to insulin therapy if HbA1c levels exceed 7.0%; and insulin therapy is intensified if patients reach the same threshold again. This is inconsistent with previous PBAC advice that in clinical practice the threshold for conversion to insulin would more likely be a HbA1c of at least 8.0% due to patients' reluctance to commence insulin (para 7.13, tirzepatide PSD, July 2023 PBAC meeting). Further, the threshold is not consistent with clinical guidelines which recommend individualising glycaemic targets based on patient-centred treatment goals.	High, favours tirzepatide
Discontinuation of GLP-1 RA on initiation of insulin	Patients must stop tirzepatide and semaglutide before switching to insulin therapy in the economic model. The resubmission acknowledged that concomitant use of GLP-1 RA/GIP therapies and insulin may occur in clinical practice, but argued that there is no evidence to support this treatment sequence, with SURPASS-5 assessing patients insufficiently controlled on insulin glargine who have tirzepatide added to their treatment regimen. The resubmission claimed that the impact of continuing treatment with insulin on HbA1c and other outcomes is unknown and cannot be included. The ESC previously considered that this assumption was inappropriate for semaglutide given that the semaglutide restriction allows concomitant therapy with insulin; and there would likely be continued use of tirzepatide alongside insulin given clinical data in this setting (SURPASS-5) and potential weight gain with insulin (Table 12, tirzepatide PSD, July 2023 PBAC meeting).	Unclear
UKPDS risk equations	The resubmission estimated drift over time in HbA1c values (and selected other biomarkers), risks of diabetes complications, and event-related mortality based on the UKPDS OM2 risk equations. The equations are based on data from a trial comparing intensive and conventional therapies for type 2 diabetes conducted in the UK between 1977 and 1997 with 10 years of additional post-trial follow-up (Leal 2021). The applicability of the equations to current Australian clinical practice was unclear given that the publication acknowledged that 'the data used to estimate the equation are increasingly historical and may in some cases reflect values or trajectories that are less commonly seen in contemporary populations'. Given this limitation, it would be appropriate to calibrate the UKPDS risk equations against more contemporary datasets, such as GLP-1 RA cardiovascular outcomes trials. The resubmission provided sensitivity analyses based on calibration factors used in the GLP-1 RA Review to calibrate the UKPDS OM2 equations to the Australian context (based on Harding 2014), which had a minimal impact on the results of the economic evaluation. However, the resubmission noted that the calibration is limited to cardiovascular outcomes only; and the results may not be representative of current clinical practice due to the age of the included Australian data (1997-2010). A comparison of HbA1c drift estimated from the economic model and from the GLP-1 RA cardiovascular outcomes trials (semaglutide trial SUSTAIN-6; dulaglutide trial REWIND) included with the resubmission indicated that the model substantially overestimates HbA1c drift.	Unclear
Weight-related disutility/utility values	The resubmission used the same approach to weight-related disutility/utility values as the July 2023 submission. Utility gains associated with weight loss in the first year of the model were derived from utility gains associated with various percentage weight reductions in obese type 2 diabetes patients from a UK vignette-based time trade-off study (Boye 2022). The resubmission used these values to calculate an average utility gain for each modelled treatment arm based on the mean change in BMI reported in the SURPASS-2 post hoc subgroup with BMI ≥35 kg/m <sup>2</sup> . The resubmission did not justify applying utility estimates	High, direction unclear

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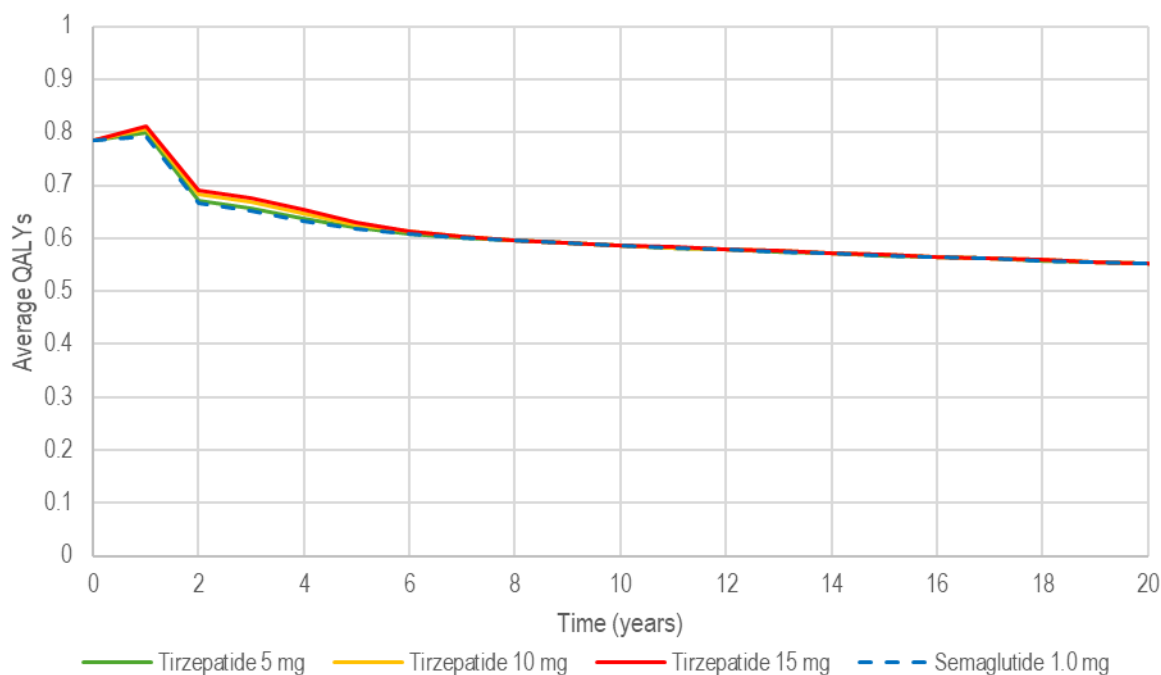
Description	Method/Value	Impact
	<p>to population-level data rather than modelled individual estimates of weight change. The approach used in the submission resulted in implausible scenarios such as patients with modelled weight gain accruing the utility benefits associated with substantial weight loss.</p> <p>The disutility associated with weight in subsequent years was based on a cross-sectional survey of European type 2 diabetes patients using the EQ-5D-3L (CODE-2 study; Bagust and Beale, 2005). This source was not adequately justified, given the substantial number of other utility/disutility values in the published literature based on absolute (per unit change in kg or BMI), categorical (normal weight, overweight, obese, morbidly obese) or relative measures (percentage change). Based on the literature search presented in the resubmission the disutility associated with a 1 unit increase in BMI can range from 0.001 (Soltoft 2009) to 0.0472 (Lane 2014). 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.</p> <p>The resubmission implemented the weight-related disutility in subsequent years as an additional utility loss for all patients with a BMI &gt;25 kg/m<sup>2</sup> regardless of baseline weight. The ESC previously considered that this approach was flawed, and double counts the utility impact of patients being overweight or obese, as the baseline utility values of patients would already include any detriments associated with baseline weight (para 6.72, tirzepatide PSD, July 2023 PBAC meeting).</p> <p>The resubmission argued that the weight-related utility/disutility estimates used in the model were 2 separate, independent quality of life impacts of changes in weight; and that the baseline utility of 0.785 from Clarke 2002 does not explicitly control for BMI and is therefore unlikely to reflect the utility loss experienced by patients with a baseline BMI ≥35 kg/m<sup>2</sup>. The PBAC previously considered that the approach to applying weight-based utility/disutility values was unreliable (para 7.15, tirzepatide PSD, July 2023 PBAC meeting).</p>	

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 RA glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; IU, international units; LDL, low density lipoprotein; PBAC, Pharmaceutical Benefits Advisory Committee; PI, product information; PSD, Public Summary document; UK, United Kingdom; UKPDS OM2, United Kingdom Prospective Diabetes Study Outcomes Model 2

6.77 A model trace of the average QALYs over time in the model is shown in Figure 1.

Figure 1: Model trace of average undiscounted QALYs over time



Source: Constructed during the evaluation using the 'A7.1\_TZP Section 3 Model' spreadsheet provided with the resubmission.

- 6.78 The modelled changes in average QALYs after one year of treatment (tirzepatide 5 mg: +0.0152, 10 mg: +0.0221; 15 mg: +0.0276; semaglutide 1 mg: +0.0060) were inconsistent with the available utility data from the SURPASS-2 whole trial population (all treatment arms: +0.04) and SURPASS-2 post hoc subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> (all treatment arms: +0.05 to +0.06). The resubmission did not address the lack of internal consistency between modelled and observed utility data.
- 6.79 The model predicted a major decline in quality of life between Year 1 and Year 2 which appeared implausible given the minimal changes in biomarkers and outcomes over this period. This decline appeared to be primarily due to the misapplication of weight-based disutility values to all patients with a BMI >25 kg/m<sup>2</sup> from the second year onwards regardless of their baseline weight. This approach double-counts the utility impact of patients being overweight or obese, as the baseline utility values of patients would already include any detriments associated with baseline weight.
- 6.80 Beyond Year 2, modelled estimates of quality of life declined in all treatment arms due to age, diabetes complications and initiation of insulin therapy (which reverted baseline weight reductions and increased the frequency of hypoglycaemia episodes). There were no apparent differences between treatment arms beyond 8 years.
- 6.81 The results of the stepped economic evaluation presented in the resubmission for the comparison of tirzepatide 15 mg and semaglutide 1 mg are presented in Table 3.8-2 of the resubmission. During the evaluation, a stepped economic evaluation was conducted from the July 2023 base case to the current resubmission base case, to

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assess the impact of changes included in the current resubmission's model. The results are presented in Table 12 below.

**Table 12: Results of the stepped economic evaluation from the July 2023 base case to the current model base case**

	Incremental cost (\$)	Incremental QALYs	ICER
<b>Tirzepatide 5 mg versus semaglutide 1 mg</b>			
July 2023 evaluation base case <sup>a</sup>	█	0.0396	█ <sup>1</sup>
Correction for mortality source error <sup>b</sup> ; updated life tables and unit costs	█	0.0404	█ <sup>1</sup>
Increase inflation factor for diabetes complication costs from 2.705 to 3.750	█	0.0404	█ <sup>1</sup>
Include biomarker drift for LDL cholesterol, HDL cholesterol, white blood cell counts, eGFR and haemoglobin	█	0.0373	█ <sup>2</sup>
Disutility associated with hypoglycaemia reduced from 0.005 to 0.003	█	0.0323	█ <sup>3</sup>
Reduce HbA1c threshold for insulin initiation and intensification from 7.5% to 7.0%	█	0.0266	█ <sup>2</sup>
Decrease tirzepatide cost based on tiered pricing (from \$█ to \$█)	█	0.0266	█ <sup>4</sup>
Update patient characteristics from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	0.0340	█ <sup>5</sup>
Update treatment effects from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	<b>0.0258</b>	█ <sup>4</sup>
<b>Tirzepatide 10 mg versus semaglutide 1 mg</b>			
July 2023 evaluation base case <sup>a</sup>	█	0.0866	█ <sup>6</sup>
Correction for mortality source error <sup>b</sup> ; updated life tables and unit costs	█	0.0879	█ <sup>6</sup>
Increase inflation factor for diabetes complication costs from 2.705 to 3.750	█	0.0879	█ <sup>6</sup>
Include biomarker drift for LDL cholesterol, HDL cholesterol, white blood cell counts, eGFR and haemoglobin	█	0.0867	█ <sup>6</sup>
Disutility associated with hypoglycaemia reduced (from 0.005 to 0.003)	█	0.0756	█ <sup>6</sup>
Reduce HbA1c threshold for insulin initiation and intensification from 7.5% to 7.0%	█	0.0623	█ <sup>6</sup>
Decrease tirzepatide cost based on tiered pricing (from \$█ to \$█)	█	0.0623	█ <sup>6</sup>
Update patient characteristics from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	0.0677	█ <sup>6</sup>
Update treatment effects from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	<b>0.0772</b>	█ <sup>7</sup>
<b>Tirzepatide 15 mg versus semaglutide 1 mg</b>			
July 2023 evaluation base case <sup>a</sup>	█	0.1143	█ <sup>7</sup>
Correction for mortality source error <sup>b</sup> ; updated life tables and unit costs	█	0.1148	█ <sup>7</sup>
Increase inflation factor for diabetes complication costs from 2.705 to 3.750	█	0.1148	█ <sup>7</sup>
Include biomarker drift for LDL cholesterol, HDL cholesterol, white blood cell counts, eGFR and haemoglobin	█	0.1115	█ <sup>7</sup>
Disutility associated with hypoglycaemia reduced (from 0.005 to 0.003)	█	0.0985	█ <sup>6</sup>
Reduce HbA1c threshold for insulin initiation and intensification from 7.5% to 7.0%	█	0.0819	█ <sup>7</sup>
Increase tirzepatide cost based on tiered pricing (from \$█ to \$█)	█	0.0819	█ <sup>6</sup>
Update patient characteristics from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	0.0930	█ <sup>6</sup>
Update treatment effects from SURPASS-2 whole trial population to post hoc subgroup with BMI ≥35 kg/m <sup>2</sup>	█	<b>0.1127</b>	█ <sup>8</sup>

Source: Constructed during the evaluation using the 'A7.1\_TZP Section 3 Model' spreadsheet 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

<sup>a</sup> Estimates from the July 2023 submission were corrected for an error in insulin dosing; included the updated price of insulin aspart; and assumed that eGFR reverts to baseline with insulin intensification for all treatment arms (the submission's base case applied inconsistent eGFR treatment effects).

<sup>b</sup> The July 2023 submission claimed that Australian life tables were used for both 'years with no event history or events' and 'years with history of events but no events', but UKPDS mortality risks were used in error for 'years with history of events but no events'.

The redacted values correspond to the following ranges:

1 \$115,000 to < \$135,000

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2 \$135,000 to < \$155,000

3 \$155,000 to < \$255,000

4 \$95,000 to < \$115,000

5 \$75,000 to < \$95,000

6 \$55,000 to < \$75,000

7 \$45,000 to < \$55,000

8 \$35,000 to < \$45,000

- 6.82 Based on the economic model, treatment with tirzepatide was associated with an incremental cost per QALY gained of \$95,000 to < \$115,000 for the 5 mg dose, \$45,000 to < \$55,000 for the 10 mg dose and \$35,000 to < \$45,000 for the 15 mg dose compared to semaglutide 1 mg weekly.
- 6.83 Compared to semaglutide 0.5 mg weekly, treatment with tirzepatide 5 mg was associated with an incremental cost per QALY gained of \$35,000 to < \$45,000.
- 6.84 The PBAC previously considered that an ICER in the order of \$30,000 per QALY would be appropriate (para 7.16, tirzepatide PSD, July 2023 PBAC meeting). However, the resubmission argued that that the proposed population is at greater risk of experiencing life-threatening diabetes-related complications, there is a high unmet need in this population for effective treatment options like tirzepatide, and it is appropriate to consider a higher ICER of \$35,000 to < \$45,000 for tirzepatide 15 mg versus semaglutide 1.0 mg. The ESC considered the subgroup of patients with severe obesity is substantial (see Table 16) and therefore does not justify the higher value proposition of a more targeted high-risk group, such as Aboriginal and Torres Strait Islander peoples.
- 6.85 Incorporating patient characteristics based on the SURPASS-2 subgroup of patients with BMI  $\geq 35$  kg/m<sup>2</sup>, and reducing the HbA1c threshold for insulin initiation and intensification (which reduced the ICER); reducing the disutility associated with hypoglycaemia, and including biomarker drift for selected biomarkers (which increased the ICER) had the largest impacts on the stepped economic evaluation from the July 2023 model to the current model for all comparisons of tirzepatide versus semaglutide 1 mg. Incorporating treatment effects based on the SURPASS-2 *post hoc* subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> increased the ICER for the tirzepatide 5 mg versus semaglutide 1 mg comparison, but decreased the ICER for the tirzepatide 10 mg and 15 mg versus semaglutide 1 mg comparisons. The higher proposed price for tirzepatide 15 mg, and lower proposed price for tirzepatide 5 mg compared to the flat price proposed in July 2023 also had a large impact on the stepped economic evaluations for the tirzepatide 15 mg versus semaglutide 1 mg and tirzepatide 5 mg versus semaglutide 1 mg comparisons, respectively.
- 6.86 For patients treated with tirzepatide 5 mg versus semaglutide 1 mg weekly and followed up for 50 years, the economic evaluation (based on undiscounted values) estimated that there would be:
- Decreased incidence of diabetes complications (40 fewer non-fatal events per 10,000 patients) and a decrease in survival (average loss of 1 day per patient).

- Decreased incidence of patients with nausea in the first year (421 fewer patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0179 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 1.1 months per patient) with a reduced incidence of hypoglycaemia events (1 fewer event per patient).
- Additional drug and administration costs of \$████ per person, but decreased diabetes complications costs of \$428 per person.

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

- Decreased incidence of diabetes complications (85 fewer non-fatal events per 10,000 patients) and an increase in survival (average gain of 1 day per patient).
- Increased incidence of patients with nausea in the first year (25 additional patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0544 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 6.0 months per patient) with a reduced incidence of hypoglycaemia events (7 fewer events per patient).
- Additional drug and administration costs of \$████ per person, but decreased diabetes complications costs of \$1,189 per person.

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

- Decreased incidence of diabetes complications (104 fewer non-fatal events per 10,000 patients) and an increase in survival (average gain of 9 days per patient).
- Increased incidence of patients with nausea in the first year (214 additional patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0792 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 7.7 months per patient) with a reduced incidence of hypoglycaemia events (9 fewer events per patient).
- Additional drug and administration costs of \$████ per person, but decreased diabetes complications costs of \$1,148 per person.

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

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
<b>Base case</b>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>2</sup>	\$ [redacted] <sup>3</sup>
<b>Discount rate (base case: 5% for benefits and costs)</b>			
3.5% discount rate	\$ [redacted] <sup>1</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)
0% discount rate	\$ [redacted] <sup>4</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)
<b>Population (base case: patient characteristics and treatment effects based on the SURPASS-2 <i>post hoc</i> subgroup with BMI ≥35 kg/m<sup>2</sup>)</b>			
Patient characteristics based on the SURPASS-2 whole trial population	\$ [redacted] <sup>1</sup> (- [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)
<b>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)</b>			
No drift for any biomarker	\$ [redacted] <sup>2</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)	\$ [redacted] <sup>3</sup> (- [redacted]%)
UKPDS drift for all biomarkers	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
<b>GLP-1 RA/GIP treatment effects (base case: tirzepatide and semaglutide treatment effects based on SURPASS-2 <i>post hoc</i> subgroup with BMI ≥35 kg/m<sup>2</sup>)</b>			
GLP-1 RA/GIP treatment effects based on the SURPASS-2 whole trial population	\$ [redacted] <sup>4</sup> (- [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
Remove HbA1c treatment effects for both arms but retain all other treatment effects	\$ [redacted] <sup>4</sup> (- [redacted]%)	\$ [redacted] <sup>4</sup> (+ [redacted]%)	\$ [redacted] <sup>4</sup> (+ [redacted]%)
Remove BMI treatment effects for both arms but retain all other treatment effects	Tirzepatide dominated (NE)	Tirzepatide dominated (NE)	Tirzepatide dominated (NE)
Remove SBP treatment effects for both arms but retain all other treatment effects	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)
<b>Insulin treatment (base case: insulin intensification steps when HbA1c &gt;7.0%; treatment effects for HbA1c and BMI based on Willis 2017; hypoglycaemia rates based on Fadini 2019)</b>			
Tirzepatide insulin initiation based on not achieving proposed continuation criteria (HbA1c <7% or HbA1c reduction ≥2%); semaglutide insulin initiation and all insulin intensification at HbA1c >7.5%	Tirzepatide dominated (NE)	\$ [redacted] <sup>4</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
Tirzepatide insulin initiation based on not achieving proposed continuation criteria (HbA1c <7% or HbA1c reduction ≥2%); semaglutide insulin initiation and all insulin intensification at HbA1c >8.0%	Tirzepatide dominated (NE)	Tirzepatide dominated (NE)	\$ [redacted] <sup>7</sup> (+ [redacted]%)
Insulin initiation and intensification at HbA1c 7.5%	\$ [redacted] <sup>1</sup> (- [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)
Insulin initiation and intensification at HbA1c 8.0%	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
Assume that semaglutide will be continued after insulin intensification (no reversion to baseline, insulin effects applied in addition to semaglutide, costs of semaglutide maintained for duration of the model) <sup>a</sup>	\$ [redacted] <sup>2</sup> savings per QALY forgone (NE)	\$ [redacted] <sup>6</sup> savings per QALY forgone (NE)	\$ [redacted] <sup>4</sup> savings per QALY forgone (NE)
Reduce insulin hypoglycaemia rate to 23 per 100 patient years (based on the SURPASS-4 trial) <sup>b,c</sup>	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
<b>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 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)</b>			
Replace baseline utility, BMI, nausea and hypoglycaemia utilities while on first-line therapy with SURPASS-2 BMI ≥35 kg/m <sup>2</sup> subgroup estimates	\$ [redacted] <sup>8</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)

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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
<b>Base case</b>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>2</sup>	\$ [redacted] <sup>3</sup>
Hypoglycaemia disutility removed	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
Hypoglycaemia disutility 0.005 (July 2023 submission base case)	\$ [redacted] <sup>9</sup> (- [redacted]%)	\$ [redacted] <sup>10</sup> (- [redacted]%)	\$ [redacted] <sup>10</sup> (- [redacted]%)
Weight-related utility/disutility removed	\$ [redacted] <sup>11</sup> (+ [redacted]%)	\$ [redacted] <sup>5</sup> (+ [redacted]%)	\$ [redacted] <sup>5</sup> (+ [redacted]%)
Subsequent weight disutility based on Soltoft 2009	\$ [redacted] <sup>12</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)	\$ [redacted] <sup>6</sup> (+ [redacted]%)
Subsequent weight disutility based on Lane 2014	\$ [redacted] <sup>9</sup> (- [redacted]%)	\$ [redacted] <sup>10</sup> (- [redacted]%)	\$ [redacted] <sup>10</sup> (- [redacted]%)
<b>Costs (base case: drug costs based on effective DPMQ, dose titration health professional visits excluded, insulin administration costs based on Diabetes Shop NSW and other assumptions, diabetes complications costs based on Clarke 2008 with CPI Medical and hospital services index adjustment)</b>			
Include GP/endocrinologist visit costs for GLP-1 RA/GIP dose titration <sup>d</sup>	\$ [redacted] <sup>1</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)
CPI Medical and hospital services index excluded	\$ [redacted] <sup>1</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)	\$ [redacted] <sup>2</sup> (+ [redacted]%)

Source: Table 3.9-2, pp254-255 of the resubmission; and 'A7.1\_TZP Section 3 Model' spreadsheet 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 RA glucagon-like peptide-1 receptor agonists; GP, general practitioner; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; ICER, incremental cost effectiveness ratio; LDL, low density lipoprotein cholesterol; NE, not estimated; QALY, quality-adjusted life year; SBP, systolic blood pressure; UKPDS OM2, United Kingdom Prospective Diabetes Study Outcomes Model 2; WBC, white blood cell.

<sup>a</sup> Note that this sensitivity analysis has no impact on HbA1c, given the model base case assumes HbA1c levels remain unaffected by patients discontinuing GLP-1 RA/GIP therapy when initiating insulin therapy.

<sup>b</sup> Reverts the disutility associated with a hypoglycaemia event to 0.005, given the disutility of 0.003 was selected based on the high frequency of hypoglycaemia events assumed in the base case (approximately monthly).

<sup>c</sup> Based on the rate per year in patients in the insulin glargine arm (without sulfonylurea) of the SURPASS-4 trial using the same hypoglycaemia definition as the SURPASS-2 trial (severe event requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose < 3.0 mmol/L).

<sup>d</sup> Includes 3 GP visits for semaglutide titration (1 level C visit (#36) \$82.90 and 2 level B visits (#23) \$42.85); 2 endocrinologist visits for tirzepatide 5 mg titration (1 initial visit (#110) \$174.50 and 1 subsequent visit (#116) \$87.30); 4 endocrinologist visits for tirzepatide 10 mg titration (1 initial visit and 3 subsequent visits); and 6 endocrinologist visits for tirzepatide 15 mg titration (1 initial visit and 5 subsequent visits).

The redacted values correspond to the following ranges:

- 1 \$95,000 to < \$115,000
- 2 \$45,000 to < \$55,000
- 3 \$35,000 to < \$45,000
- 4 \$75,000 to < \$95,000
- 5 \$115,000 to < \$135,000
- 6 \$55,000 to < \$75,000
- 7 > \$1,055,000
- 8 \$355,000 to < \$455,000
- 9 \$25,000 to < \$35,000
- 10 \$5,000 to < \$15,000
- 11 \$255,000 to < \$355,000
- 12 \$135,000 to < \$155,000

6.90 The results of the sensitivity analyses indicated that the model was most sensitive to baseline patient characteristics, biomarker drift factors, HbA1c and BMI treatment effects, incorporating the proposed tirzepatide continuation criteria (with a higher HbA1c threshold for insulin initiation for semaglutide which does not have continuation criteria; and a higher HbA1c threshold for subsequent insulin intensification), using trial-based utilities for first-line therapy, hypoglycaemia rates with insulin, hypoglycaemia and weight-related utility values, as well as the use of concomitant semaglutide with insulin.

- 6.91 Given the limited differences in clinical outcomes between tirzepatide and semaglutide (weight, adverse events, diabetes complications), the model was largely driven by differences between treatments in the time to insulin therapy (as insulin is associated with substantially worse weight and hypoglycaemia outcomes).
- 6.92 The ESC advised that the economic evaluation as presented may not provide a basis for the PBAC to recommend tirzepatide for the proposed population. The ESC considered the ICER remained uncertain and higher than previously advised would be acceptable in this indication.
- 6.93 The ESC advised 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 BMI  $\geq 35$  kg/m<sup>2</sup> subgroup estimates, or removing some of the utility effects from weight gain/loss in year one to account for potential double counting.

- 6.94 The pre-PBAC response provided a revised base case that included:
- Switching to insulin/insulin intensification when HbA1c > 7.5%;
  - Systolic blood pressure (SBP), heart rate and BMI remaining constant while on either tirzepatide or semaglutide. UKPDS biomarker drift applied for BMI, SBP and heart rate while on insulin;
  - A price reduction for all doses of tirzepatide (see paragraph 3.2).

The pre-PBAC response stated the revised base case resulted in an ICER of \$45,000 to < \$55,000 per QALY gained for tirzepatide 15 mg versus semaglutide 1.0 mg. The ICERs for the comparison of tirzepatide 10 mg versus semaglutide 1 mg and tirzepatide 5 mg versus semaglutide 1 mg were \$45,000 to < \$55,000 per QALY gained and \$75,000 to < \$95,000 per QALY gained respectively. The pre-PBAC response maintained that the proposed population are of sufficiently high unmet need to warrant an ICER of \$45,000 to < \$55,000 per QALY gained. The PBAC noted that raising insulin initiation/intensification to HbA1c > 8.0% and applying UKPDS biomarker drift for all biomarkers in the pre-PBAC response model increased the ICERs for the comparison of tirzepatide 15 mg versus semaglutide 1 mg, tirzepatide 10 mg versus semaglutide 1 mg and tirzepatide 5 mg versus semaglutide 1 mg to \$55,000 to < \$75,000 per QALY gained, \$55,000 to < \$75,000 per QALY gained and \$115,000 to < \$135,000 per QALY gained respectively.

**Drug cost/patient/year**

- 6.95 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 × 365.25 days per year).
- 6.96 The estimated drug costs per patient per year for tirzepatide are summarised in Table 14. For patients using the 15 mg strength, the estimated drug cost for tirzepatide per patient per year was higher than the July 2023 PBAC submission (\$ [REDACTED] vs \$ [REDACTED]).

**Table 14: 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% <sup>a</sup> 10 mg: 93.4% <sup>a</sup> 15 mg: 94.7% <sup>a</sup>	100% for all doses	100% for all doses
Cost per year <sup>b</sup>	-	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: 76% <sup>c</sup> Year 3: 59% <sup>c</sup> Year 4: 35% <sup>c</sup> Year 5: 14% <sup>c</sup> Year 6: 4% <sup>c</sup>	Year 2: 91% <sup>d</sup> Year 3: 83% <sup>d</sup> Year 4: 75% <sup>d</sup> Year 5: 69% <sup>d</sup> Year 6: 62% <sup>d</sup>

Source: constructed during the evaluation using the Section 3 Model and Section 4 Model, Excel workbooks of the resubmission

<sup>a</sup> Based on the proportion of patients taking at least 75% of required doses.

<sup>b</sup> Cost per year for persistent patients

<sup>c</sup> Based on proportion of patients on treatment at the start of each year, incorporating discontinuation due to death. Weighted estimates were calculated using the fixed dose distribution used in the budget impact analysis.

<sup>d</sup> Based on a fixed yearly persistence rate of 91.02%

Note that the results presented in Table 14 are derived from ad-hoc/post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.97 Treatment persistence in the economic model was based on a switch to insulin threshold of HbA1c >7.0% with modelled HbA1c drift over time based on UKPDS data, while persistence in the financial estimates was based on the proportion of patients achieving HbA1c <7.0% at 40 weeks in the trial. The ESC noted that the two approaches lead to significantly different patterns of use, and believed that neither approach is likely to be applicable to the circumstances of use of tirzepatide in clinical practice.
- 6.98 The pre-PBAC response offered a price reduction with effective DPMQs of \$ [REDACTED] for the 2.5 mg and 5 mg doses, \$ [REDACTED] for the 7.5 mg and 10 mg doses, and \$ [REDACTED] for the 12.5 mg and 15 mg doses (see paragraph 3.2).

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

6.99 This resubmission was not considered by DUSC.

6.100 The resubmission used a mixed epidemiological/market share approach to estimate the utilisation and financial implications of listing tirzepatide on the PBS/RPBS for the treatment of type 2 diabetes based on four mutually exclusive subgroups:

- Established eligible patients with type 2 diabetes and BMI  $\geq 35$  kg/m<sup>2</sup>.
- Newly eligible patients with type 2 diabetes and BMI  $\geq 35$  kg/m<sup>2</sup>.
- Established eligible Aboriginal and Torres Strait Islander peoples with type 2 diabetes and BMI  $<35$  kg/m<sup>2</sup>.
- Newly eligible Aboriginal and Torres Strait Islander peoples with type 2 diabetes and BMI  $<35$  kg/m<sup>2</sup>.

6.101 During the evaluation, the sponsor identified an error in the parameterisation of the 10% PBS sample analysis that formed the basis of the utilisation and financial estimates. The sponsor provided an updated analysis and financial estimates model with corrections for this error. All utilisation and financial estimates were revised accordingly.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Patients who switched out of SGLT2i	<p>Established eligibility: █<sup>1</sup> (cumulative over 6 years between 2019-2024).</p> <p>Newly eligible: █<sup>2</sup> in Year 1 increasing to █<sup>2</sup> in Year 6.</p> <p>Sponsor-commissioned 10% PBS sample analysis. Estimated based on patients treated for type 2 diabetes with an SGLT2i (including combinations with metformin, DPP4i or sulfonylurea, excluding insulin and GLP-1 RAs) who switched to another therapy (including GLP-1 RAs, DPP4i, metformin, sulfonylurea and insulin).</p>	<p>Regimens included in the analysis did not appear to align with prior therapy requirements in the proposed restriction (e.g. included SGLT2i monotherapy, excluded SGLT2i in combination with insulin).</p> <p>The PSCR confirmed that monthly proportion of patients who switched out/dropped off SGLT2i therapy in the 10% PBS sample analysis were representative of unique patients and not episodes of care. However, the ESC noted the estimated proportion of patients who switched out/dropped off SGLT2i therapy (68%) over the 5-year analysis period appeared high.</p> <p>The 10% PBS sample analysis indicated instability in SGLT2i switch outs from 2022-2023 (marked increase then decrease), which may be a flow-on consequence of GLP-1 RA shortages. This introduced added uncertainty in extrapolated estimates. The pre-PBAC response adjusted the starting point for extrapolating the newly eligible incident population to October 2022 with linear extrapolation applied.</p> <p>The assumed duration of established eligibility based on patients with changes in therapy up to 6 years prior may not be reasonable as it does not account for patients who achieve adequate response following initiation of other therapies. The pre-PBAC response changed the assumed duration of established eligibility of prevalent patients from 6 years to 3 years prior to the first PBS listing.</p>
Patients with type 2 diabetes and eGFR <30	<p>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).</p>	<p>CKD prevalence estimates in the US setting may not be applicable to the Australian setting due to differences in population characteristics.</p>
Patients who switched out of metformin monotherapy due to eGFR <30	<p>Established eligibility: █<sup>3</sup> (cumulative over 6 years between 2019-2024).</p> <p>Newly eligible: █<sup>4</sup> in Year 1 increasing to █<sup>4</sup> in Year 6.</p> <p>Sponsor-commissioned 10% PBS sample analysis. Estimated based on patients who switched out of metformin monotherapy to non-SGLT2i therapy (i.e. GLP-1 RA, DPP4i, insulin, acarbose, sulfonylurea, thiazolidinedione). Patient estimates were multiplied by the proportion of patients with eGFR &lt;30 (3.1%, see above).</p>	<p>It was unclear whether metformin monotherapy switch outs were representative of unique patients or episodes of care due to inconsistencies in the information provided by the sponsor.</p> <p>The assumed duration of established eligibility based on patients with changes in therapy up to 6 years prior may not be reasonable as it does not account for patients who achieve adequate response following initiation of other therapies.</p> <p>CKD prevalence among the general type 2 diabetes population may not be applicable to patients who switched out of metformin monotherapy.</p>

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Parameter	Value applied and source	Comment
Patients on GLP-1 RA without prior SGLT2i treatment	█████ <sup>2</sup> . Sponsor-commissioned 10% PBS sample analysis. Estimated based on patients treated with GLP-1 RA (alone or in combination with any other therapy) without prior use of SGLT2i, prior to the June 2024 restriction changes.	The analysis, based on GLP-1 RA grandfathering provisions, was inconsistent with the proposed grandfathering provisions for tirzepatide that require patients to meet the same criteria as the proposed initial restriction. The inclusion of these estimates would overestimate the size of the eligible population. The PSCR proposed the addition of a clinical criterion to the initial treatment restriction, which would enable patients treated with a GLP-1 RA prior to June 2024 restriction change to switch to tirzepatide. Details of this proposal were not presented.
Proportion of patients with type 2 diabetes and BMI ≥35 kg/m <sup>2</sup>	42%. Retrospective analysis of data from adult patients with type 2 diabetes who attended a specialist diabetes outpatient service in Sydney between 2017 and 2019 (Thakur 2021). Of the 700 people seen in the service, 291 (42%) had BMI ≥35 kg/m <sup>2</sup> .	The applicability of these estimates was uncertain given the relatively small sample from a single centre. The study was also conducted in a broader population, which is unlikely to be applicable to patients who meet prior therapy criteria in the proposed restriction.
Uptake rate in patients with established eligibility	█████% within 3 years (Year 1: █████%, Year 2: █████%, Year 3: 10%). Assumed in the resubmission accounting for access to endocrinologists.	Uptake estimates appeared optimistic given the proposed restriction is more stringent compared to the current GLP-1 RA restriction in terms of authority level, prescriber, treatment regimen (dual therapy with metformin only), continuing treatment criteria and administrative requirements. The estimates also appear optimistic given the expected size of the population requiring access to endocrinologists.  The assumption that the vast majority of patients with established eligibility based historical treatment patterns (up to 6 years prior) would be considered suitable for treatment with tirzepatide as dual therapy with metformin only was inadequately justified.
Uptake rate in newly eligible patients	Year 1: █████%, Year 2: █████%. Years 3-6: █████%. Based on a survey of clinicians in the sponsor's advisory board, where █████% of respondents indicated that they would prescribe a GIP/GLP-1 RA in the majority of patients who have trialled an SGLT2i.	Uptake estimates appeared optimistic given the proposed restriction is more stringent compared to the current GLP-1 RA restriction. The estimates also appear optimistic given the expected size of the population requiring access to endocrinologists. The ESC noted the financial estimates were highly sensitive to the assumed uptake rates.
Adherence	100%. Assumed.	This was inconsistent with trial data indicating imperfect adherence in the trial depending on dose (5 mg: 95.7%, 10 mg: 93.4%, 15 mg: 94.7%). The ESC considered adherence in practice is likely to be lower than observed in the trial. The pre-PBAC response reduced the adherence rate from 100% to 93%.

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Parameter	Value applied and source	Comment
Persistence	<p>100% in Year 1 then 91.02%<sup>a</sup> every year thereafter. The resubmission claimed the proportion of patients achieving HbA1c &lt;7.0% in trial would be a reasonable proxy for persistence given continuing treatment criteria in the proposed restriction. Data from the subgroup with BMI ≥35 kg/m<sup>2</sup> and the dose distribution used in the resubmission (see below) were used to calculate a weighted response estimate.</p> <p>The weighted response estimate was applied as a persistence rate, kept constant in each year. The resubmission claimed that this was reasonable given the same approach based on the semaglutide 1 mg arm would result in 53%<sup>a</sup> of patients remaining on treatment in Year 3, similar to length of treatment estimates in the June 2024 DUSC review of semaglutide (median length of treatment of 3 years for patients on GLP-1 RAs). The resubmission noted that the proportion of patients remaining on tirzepatide in Year 3 was higher (75%<sup>b</sup>) but claimed that this was expected given higher response rates for tirzepatide compared to semaglutide 1 mg.</p>	<p>The resubmission's approach was reliant on the assumption that treatment discontinuations would only occur due to inadequate response and that improved treatment response with tirzepatide would result in improved persistence compared to semaglutide. In practice, persistence with tirzepatide is likely to be lower compared to GLP-1 RAs given the likelihood of increased adverse events with higher doses, the proposed treatment continuation criteria and allowed use as dual therapy with metformin only.</p> <p>The resubmission's estimate does not account for adequate response based on a reduction in HbA1c of at least 2%, as per the proposed restriction.</p> <p>The use of a weighted estimate assumes no difference in persistence across tirzepatide doses which was inconsistent with key trial data.</p> <p>The use of a constant rate was inadequately justified. It may not be appropriate to align persistence estimates with length of treatment estimates in the DUSC analysis as the DUSC analysis did not account for breaks in treatment (e.g. a patient supplied dulaglutide once, followed by semaglutide 3 years later would have a time on treatment of more than 3 years). Additionally, the DUSC analysis would include discontinuations due to reasons other than inadequate treatment response.</p> <p>Persistence estimates used in the budget impact analysis were considerably higher than applied in the economic model (see Table 14 above). The pre-PBAC response corrected an error in the calculation of persistence and proposed a constant persistence rate of 91.08%<sup>a</sup>. The pre-PBAC response noted that application of the revised persistence rate resulted in around 57%<sup>a</sup> of patients remaining on tirzepatide treatment at year 6.</p>
Tirzepatide dose distribution	<p>5 mg: ■■■%, 10 mg: ■■■%, 15 mg: ■■■%. Based on sponsor-commissioned market research data. The dose distribution was informed by responses to a survey of endocrinologists regarding target maintenance doses for tirzepatide.</p>	<p>The applicability of target maintenance doses to doses used in practice is uncertain, with survey respondents noting that dose titration would be influenced by a range of factors including treatment response and tolerability. Differences in the utilisation of these doses in practice will have financial implications given the tiered pricing structure.</p> <p>The financial estimates did not include the use of titration doses (2.5 mg, 7.5 mg, 12.5 mg).</p>
GLP-1 RA script substitution rate	100%. Assumption.	<p>The assumed 1:1 script substitution rate was inconsistent with the resubmission's argument of higher persistence rates with tirzepatide compared with semaglutide and modelled differences in persistence in the economic model.</p>

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Source: Section 4.1, pp260-275 of the resubmission; Tirzepatide Section 4 updated Excel workbook, Attachments A1, A2, A5.3 and A8.3 provided by the sponsor during the evaluation

Abbreviations: CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate (mL/min/1.72 m<sup>2</sup>); GLP-1 RA, glucagon-like peptide-1 receptor agonist; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SGLT2i, sodium-glucose cotransporter-2 inhibitor

<sup>a</sup> Note that the results presented in Table 15 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

The redacted values correspond to the following ranges:

<sup>1</sup> 400,000 to < 500,000

<sup>2</sup> 100,000 to < 200,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> 500 to < 5,000

6.102 The estimated utilisation and financial implications (using effective prices) of listing tirzepatide on the PBS/RPBS for the treatment of type 2 diabetes is summarised in Table 16. The revised financial estimates provided in the pre-PBAC response are also provided in Table 16. The revisions made in the pre-PBAC response are outlined in Table 15 and also include the price reductions stated in paragraph 3.2.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Patients with BMI ≥35 kg/m<sup>2</sup></b>						
Initiating patients	1	1	2	3	4	4
- Established eligible	1	3	5	-	-	-
- Newly eligible	6	7	3	3	4	4
Continuing patients	-	1	8	9	9	9
Total patients	1	8	9	9	10	10
<b>Aboriginal and Torres Strait Islander peoples with BMI &lt;35 kg/m<sup>2</sup></b>						
Initiating patients	11	11	12	12	12	12
- Established eligible	11	13	12	-	-	-
- Newly eligible	12	12	12	12	12	12
Continuing patients	-	11	11	5	5	5
Total patients	11	11	5	5	5	5
<b>Estimated extent of use</b>						
Total patients	1	9	9	10	10	10
- 5 mg dose (1%)	14	15	16	16	16	16
- 10 mg dose (1%)	15	16	16	16	17	17
- 15 mg dose (1%)	16	16	17	17	17	17
Total scripts	17	18	18	18	18	19
July 2023 submission total tirzepatide scripts	20	16	16	17	17	17
Change from July 2023	348%	253%	248%	228%	226%	225%
<b>Estimated financial impact</b>						
Cost to PBS/RPBS cost less copayments	21	22	23	23	23	23
Cost offset less copayment, substituted semaglutide/dulaglutide	24	24	24	24	24	24
<b>Net PBS/RPBS cost</b>	25	21	27	27	28	22
<b>Pre-PBAC response</b>						
Cost to PBS/RPBS less copayments	25	26	27	27	28	22
Cost offset less copayment, substituted semaglutide/dulaglutide	24	24	24	24	24	24
<b>Net PBS/RPBS cost</b>	29	30	25	25	26	26
July 2023 submission net PBS/RPBS cost	31	29	30	30	25	25
Change from July 2023	356%	259%	255%	233%	231%	230%

Source: Tirzepatide Section 4\_updated model Excel workbook provided by the sponsor during the evaluation, Table 5 pre-PBAC response

Note: All estimates were updated by the sponsor during the evaluation due to an identified error in the 10% PBS sample analysis

The redacted values correspond to the following ranges:

- 1 100,000 to < 200,000
- 2 80,000 to < 90,000
- 3 60,000 to < 70,000
- 4 70,000 to < 80,000
- 5 20,000 to < 30,000
- 6 40,000 to < 50,000
- 7 50,000 to < 60,000
- 8 200,000 to < 300,000
- 9 300,000 to < 400,000
- 10 400,000 to < 500,000
- 11 10,000 to < 20,000
- 12 500 to < 5,000

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- 13 5,000 to < 10,000
- 14 \$500,000 to < 600,000
- 15 800,000 to < 900,000
- 16 1,000,000 to < 2,000,000
- 17 2,000,000 to < 3,000,000
- 18 4,000,000 to < 6,000,000
- 18 6,000,000 to < 7,000,000
- 20 700,000 to < 800,000
- 21 \$500 million to < \$600 million
- 22 \$800 million to < \$900 million
- 23 > \$1 billion
- 24 net cost saving
- 25 \$300 million to < \$400 million
- 26 \$400 million to < \$500 million
- 27 \$600 million to < \$700 million
- 28 \$700 million to < \$800 million
- 29 \$100 million to < \$200 million
- 30 \$200 million to < \$300 million
- 31 \$90 million to < \$100 million

- 6.103 The net cost the PBS/RPBS was \$300 million to < \$400 million in Year 1, increasing to \$800 million to < \$900 million in Year 6, with a cumulative net cost of > \$1 billion over the first 6 years of listing. The pre-PBAC response provided revised financial estimates which reported the net cost to the PBS/RPBS of \$100 million to < \$200 million in Year 1, increasing to \$400 million to < \$500 million in Year 6, with a cumulative net cost of > \$1 billion over the first 6 years of listing. The net PBS/RPBS cost in the pre-PBAC response was lower than estimated in the resubmission primarily due to a reduction in the estimated size of the eligible population (based on historical SGLT2i use up to October 2022 with linear extrapolation; established eligibility based on prior 3 years instead of 6 years). There were additional changes due to a reduction in the proposed effective price of tirzepatide and a number of minor changes to other inputs (estimated size of subset of patients with established eligibility based on historical use of GLP-1 RA, persistence rate, tirzepatide adherence rate and GLP-1 RA adherence rate).
- 6.104 The net PBS/RPBS cost in the current resubmission was substantially higher (247%) than in the July 2023 submission (previously > \$1 billion over 6 years) primarily due to a larger treated population despite the narrower requested population. The revised financial estimates provided in the pre-PBAC response remained substantially higher (140%) than in the July 2023 submission. However, the PBAC previously noted limitations with estimates in the July 2023 submission that were largely uninformative as they were based on historical trends for GLP-1 RA therapies which were unlikely to reflect future use (para 6.92, tirzepatide PSD, July 2023 PBAC meeting).
- 6.105 The estimated net PBS/RPBS cost of listing tirzepatide for type 2 diabetes was highly uncertain for the following reasons:
- The size of the eligible population was estimated based on historical circumstances of use of type 2 diabetes medications which may not reflect future utilisation of these therapies. There have been multiple changes in PBS

restrictions for type 2 diabetes medications over time as well as changing treatment algorithms that are likely to affect future patterns of treatment.

- The budget impact analysis does not account for concomitant use of SGLT2 inhibitors for chronic kidney disease or heart failure, which is allowed under the proposed restriction. The PSCR considered this population is small as data from the Australian Institute of Health and Welfare reported that around 13.4% of patients have type 2 diabetes and comorbid chronic kidney disease or cardiovascular disease (AIHW Chronic Kidney Disease Facts, June 2024). The ESC noted this estimate was based on the general population with type 2 diabetes. The size of this population likely to be larger in the requested PBS population as the presence of these comorbidities is likely to be higher in this subgroup, as indicated by data presented in the resubmission.
- The GIP/GLP-1 RA market was subject to ongoing supply constraints resulting from strong demand for these treatments globally. The TGA noted limited supply of semaglutide and dulaglutide with a supply impact date until 31 December 2024, and limited supply of tirzepatide with a supply impact date until 31 August 2024. The supply shortages had resulted in an unstable market for GLP-1 RAs, with flow-on impacts on the utilisation of other type 2 diabetes medications including SGLT2 inhibitors on the PBS.
- The ESC considered there was high risk of use beyond the narrow requested population, given the clinical trial evidence and treatment guidelines support use in broader populations, as well as the risk of ongoing use in patients not meeting continuing treatment criteria. The ESC considered the high demand for tirzepatide in the private market (including as an alternative to semaglutide due to supply shortages) increased the risk of use outside the restriction. The degree to which this is mitigated by the proposed restriction was uncertain.
- The estimated size of the eligible population meeting prior therapy criteria in the proposed restriction was highly uncertain due to limitations with data sources and methods applied in the resubmission. In particular, it was unclear whether estimates from the 10% PBS sample represented unique patients or episodes of care.
- The resubmission assumed that patients treated with GLP-1 RA prior to the June 2024 restriction changes would be eligible for tirzepatide based on GLP-1 RA grandfathering provisions, which was inconsistent with criteria in the proposed grandfathering provisions for tirzepatide. The inclusion of these estimates was inappropriate and would overestimate the size of the eligible population. The PSCR clarified that the proposed population for grandfathering are a small group of patients who are currently purchasing non-PBS-subsidised tirzepatide in the private market and who met the clinical criteria for tirzepatide at treatment initiation. The PSCR considered grandfathering arrangements were critical for this group as the proposed high-

risk target populations are likely to have a lower socioeconomic status with limited financial resources. The PSCR also proposed the addition of a clinical criterion to the initial treatment restriction, which would enable patients treated with a GLP-1 RA prior to June 2024 restriction change to switch to tirzepatide. Details of this proposal were not presented.

- Uptake rates in the established eligible and newly eligible populations appeared optimistic given the proposed restriction is more stringent compared to the current GLP-1 RA restriction in terms of authority level, prescriber, treatment regimen (dual therapy with metformin only), continuing treatment criteria and administrative requirements. The estimated size of the patient population requiring access to endocrinologists for treatment initiation appeared large. The pre-PBAC response argued that with the amendment of the requirement for endocrinologist initiation (see paragraph 3.9) the high uptake rates were reasonable.
- The circumstances of use of tirzepatide (fixed dose distribution, perfect adherence, constant persistence rate based on maintenance of HbA1c <7.0% only) may not reflect Australian clinical practice (flexible titration, imperfect adherence and imperfect persistence due to a broad range of factors). Persistence estimates in the budget impact model were considerably higher than applied in the economic model.
- Cost offsets due to substitution of GLP-1 RAs were estimated using a 100% script substitution rate. This was inconsistent with the resubmission's arguments of improved persistence with tirzepatide treatment compared to GLP-1 RAs and modelled differences in persistence in the economic model.

6.106 The resubmission had not accounted for increased MBS costs associated with endocrinologist visits for treatment initiation of tirzepatide. This was inappropriate given increased costs associated with a higher number of visits for the titration regimen of tirzepatide (up to 6 visits to achieve the 15 mg dose) compared to GLP-1 RAs (up to 3 visits to achieve the semaglutide 1 mg dose). Additionally, treatment with GLP-1 RAs can be initiated by GPs with lower MBS costs per visit compared to endocrinologists.

6.107 Table 17 is a summary of key sensitivity analyses presented in the resubmission and conducted during the evaluation.

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Table 17: Budget impact sensitivity analyses

Sensitivity analysis	Net PBS/RPBS cost over 6 years
Revised base case (corrected by sponsor using a 180-day treatment window for insulin in the 10% PBS sample analysis)	█ <sup>1</sup>
Resubmission's base case (60-day treatment window for insulin in the 10% PBS sample analysis)	█ <sup>1</sup>
Eligible population (base case combined subgroups with BMI ≥35 kg/m <sup>2</sup> and Aboriginal and Torres Strait Islander peoples with BMI <35 kg/m <sup>2</sup> )	
- Patients with BMI ≥35 kg/m <sup>2</sup> only	█ <sup>1</sup>
- Aboriginal and Torres Strait Islander peoples only (assuming 100% are eligible)	█ <sup>2</sup>
Duration of established eligibility (base case includes patients meeting prior therapy criteria in the 6 years prior)	
- 3 years prior <sup>a</sup>	█ <sup>1</sup>
- 1 year prior <sup>b</sup>	█ <sup>1</sup>
10% PBS sample analysis for SGLT2i and metformin monotherapy switch outs (base case 6-month treatment window)	
- 3-month treatment window <sup>c</sup>	█ <sup>1</sup>
- 12-month treatment window <sup>d</sup>	█ <sup>1</sup>
10% PBS sample analysis for SGLT2i and metformin monotherapy switch outs and drop-offs (base case switch outs only)	
- Include SGLT2i and metformin monotherapy drop-offs <sup>e</sup>	█ <sup>1</sup>
Proportion of patients with BMI ≥35 kg/m <sup>2</sup> (base case 42%)	
- 50%	█ <sup>1</sup>
- 30%	█ <sup>1</sup>
Grandfathered population based on population treated with GLP-1 prior to 1 June 2024 (base case estimate █ <sup>3</sup> )	
- Remove, assuming these patients are not eligible	█ <sup>1</sup>
Uptake rate in established eligible population (base case █% in 3 years)	
- █% in 3 years	█ <sup>1</sup>
- █% in 3 years	█ <sup>1</sup>
Uptake rate in newly eligible population (base case █% year 1, █% year 2, █% years 3-6)	
- █% year 1, █% year 2, █% years 3-6	█ <sup>1</sup>
- █% year 1, █% year 2, █% years 3-6	█ <sup>1</sup>
Persistence rate (base case constant rate of 91.02%)	
- Variable persistence rate (90% year 2, 85% year 3, 80% year 4, 75% year 5, 70% year 6)	█ <sup>1</sup>
- Persistence rate based on the economic model, patients on treatment if their HbA1c <7.0% (76% year 2, 78% year 3, 60% year 4, 41% year 5, 27% year 6) <sup>f</sup>	█ <sup>1</sup>
- Persistence rate based on the economic model, on treatment if their HbA1c <7.0% or they have a change in HbA1c ≥2.0% from baseline (80% year 2, 79% year 3, 60% year 4, 40% year 5, 27% year 6) <sup>f</sup>	█ <sup>1</sup>

Source: Table 4.6-1, p285 of the resubmission and Tirzepatide Section 4\_updated model Excel workbook provided by the sponsor during the evaluation

Abbreviations: BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PBS, Pharmaceutical Benefits Scheme; SGLT2i, sodium-glucose cotransporter-2 inhibitor

<sup>a</sup> Reduces the proportion of patients who meet prior therapy criteria in the Aboriginal and Torres Strait Islander population to 27.7%

<sup>b</sup> Reduces the proportion of patients who meet prior therapy criteria in the Aboriginal and Torres Strait Islander population to 13.0%

<sup>c</sup> Increases the proportion of patients who meet prior therapy criteria in the Aboriginal and Torres Strait Islander population to 48.6%

<sup>d</sup> Reduces the proportion of patients who meet prior therapy criteria in the Aboriginal and Torres Strait Islander population to 32.4%

<sup>e</sup> Increases the proportion of patients who meet prior therapy criteria in the Aboriginal and Torres Strait Islander population to 50.6%

<sup>f</sup> Estimated during the evaluation based on proportions of patients on treatment at the start of Year 2 (converted to persistence rates), weighted using the fixed tirzepatide dose distribution in the resubmission (5 mg: █%, 10 mg: █%, 15 mg: █%)

Note that the results presented in Table 17 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study SURPASS-2. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

The redacted values correspond to the following ranges:

1 > \$1 billion

2 \$200 million to < \$300 million

3 100,000 to < 200,000

- 6.108 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), duration of established eligibility, proportion of patients with BMI  $\geq 35$  kg/m<sup>2</sup>, inclusion of the grandfathered population treated with GLP-1 RA, persistence rate and uptake rates. None of these estimates were adequately supported in the resubmission.
- 6.109 Although the resubmission was targeted towards a narrower population than the previous submission, the estimated utilisation of tirzepatide and net cost to the PBS and RPBS had more than doubled. The ESC considered the estimated utilisation and financial estimates were extremely high and uncertain and not sufficiently reliable for PBAC decision-making. The pre-PBAC response provided revised lower financial estimates (see paragraph 6.103).

### ***Quality Use of Medicines***

- 6.110 The resubmission stated that the sponsor would continue with current educational activities to healthcare providers to ensure safe and appropriate use of tirzepatide for type 2 diabetes. The sponsor was also undertaking pharmacovigilance activities to manage any safety risks associated with tirzepatide treatment.
- 6.111 Expert advice provided with the resubmission raised concerns regarding the need for pharmacies to stock the array of doses as well as concerns about the reliable supply in order to allow for appropriate dose titration.
- 6.112 The resubmission did not address the potential for medication errors given the array of doses and multiple formulations of tirzepatide proposed for listing. There may be greater potential for error or misuse with the availability of the multi-dose pen.
- 6.113 The ESC considered that there was a risk that PBS-listed tirzepatide could be diverted (provided to people not prescribed tirzepatide) due to its effect on weight loss.

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

- 6.114 No risk sharing arrangements (RSA) were proposed in the resubmission. The PSCR suggested that no RSA would be required due to the proposed narrower restrictions, which includes provision of recent HbA1c pathology results (via written Authority). The ESC did not consider this reasonable or amenable to providing Government with assurance of its estimated future PBS expenditure for this extremely high-cost medicine, and given the high risk of use outside the restriction into the chronic weight management indication. However, the ESC also considered the financial estimates provided in the resubmission were not sufficiently robust to be used for an RSA. Further detail and revision of the budget impact model was required: to provide more confidence around interpretation of the 10% sample analysis underpinning the eligible population (and the extrapolation into future years); and to review assumptions around uptake and maintenance which appear high and collectively drive up the total cost.

6.115 The pre-PBAC response stated that given the associated risk to both Commonwealth (increased expenditure) and sponsor (opportunity cost of private market revenue), the sponsor was open to collaborating with the department to identify additional initiatives that are focused on controlling utilisation. The pre-PBAC response proposed an RSA based on the following elements:

- Subsidisation caps based on the revised Commonwealth Expenditure price and Section 4 model;
- Subsidisation cap 1 (SC1) based on the estimated utilisation for the proposed population. For expenditure above SC1 a rebate of [REDACTED]% was proposed based upon the [REDACTED] [REDACTED] required to achieve an ICER of \$25,000 to < \$35,000 per QALY in the broader diabetes population not limited by BMI≥35kg/m<sup>2</sup>.
- Subsidisation cap 2 (SC2) was based upon the broader diabetes population not limited by BMI≥35kg/m<sup>2</sup> with a rebate of [REDACTED]% for expenditure above SC2 based upon [REDACTED] [REDACTED] sharing of any financial risk and ensuring that [REDACTED] [REDACTED] price of tirzepatide does not [REDACTED] [REDACTED] the level of GLP-1 RA.

The pre-PBAC response proposed the option of a [REDACTED] deed of agreement with an assessment of utilisation after this time.

**Table 18 Proposed subsidisation cap (SC) structure for tirzepatide (effective AEMP)**

	Year 1 (2025) <sup>a</sup>	Year 2 (2026) <sup>a</sup>	Year 3 (2027) <sup>a</sup>	Year 4 (2028) <sup>a</sup>	Year 5 (2029) <sup>a</sup>
SC1 <sup>b</sup> (\$)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SC2 (\$)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Table 6 pre-PBAC response.

Note: Table 6 footnote states the source as Attachment A8.1\_Tirzepatide Section 4\_revised (Pre-PBAC) – Tab 3c. Impact – proposed (eff)

[REDACTED]

Abbreviations: AEMP = approved ex-manufacturer price, SC= subsidisation cap

<sup>a</sup> Based on effective AEMP-based Commonwealth expenditure.

<sup>b</sup> There is no discount applied up to the specified SC1, and a [REDACTED]% discount is applied beyond SC1 and a [REDACTED]% rebate beyond SC2.

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

## 7 PBAC Outcome

7.1 The PBAC did not recommend tirzepatide for the treatment of adult patients with inadequately controlled type 2 diabetes mellitus (T2DM) who (i) have comorbid severe obesity or (ii) identify as Aboriginal and Torres Strait Islander. The PBAC considered that tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly were superior in terms of effectiveness for glycaemic benefits and short-term weight loss compared to semaglutide 1 mg once weekly in the target subgroup with severe obesity, but advised this claim was not supported for tirzepatide 5 mg once weekly compared to semaglutide 1 mg once weekly. The PBAC considered the non-inferior safety claim was not adequately supported for any of the comparisons. The PBAC noted the resubmission provided a revised economic model with further amendments to the model provided in the pre-PBAC response along with a price reduction. The PBAC considered the pre-PBAC response economic model did not adequately address the concerns raised by the Committee in July 2023 or the subsequent concerns raised by

the ESC in this consideration. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high, inadequately justified, and uncertain. The PBAC advised that a revised economic model including a price reduction would be required for the proposed listing to be considered cost-effective. The PBAC noted the financial impact was extremely high at the prices proposed in the pre-PBAC response, although considered it likely overestimated. The PBAC considered the risk sharing arrangements (RSA) proposed in the pre-PBAC response were unlikely to satisfactorily mitigate the risk to government of use outside of the proposed restriction.

- 7.2 The PBAC noted the comments from individuals, health care professionals and organisations which, consistent with the July 2023 submission consumer comments, highlighted benefits of treatment with tirzepatide including significant reduction in glycosylated haemoglobin (HbA1c) and weight loss. The consumer comments noted significant barriers to access that have been experienced with existing GLP-1 RA medications and the potential advantages of having alternative treatment options available to address supply concerns. The PBAC noted the concerns raised by health care professionals, Diabetes Australia and National Aboriginal Community Controlled Health Organisation (NACCHO) that the resubmissions proposal to require the involvement of an endocrinologist in the prescribing of tirzepatide would be a barrier to access. The PBAC considered there was no clinical reason for the treatment criteria to be different to that of semaglutide and agreed with the concerns raised that this may result in an inappropriate barrier for prescribing of tirzepatide.
- 7.3 The PBAC advised the resubmission's proposed narrower T2DM restriction, based on patients with inadequately controlled T2DM and who either have a body mass index (BMI)  $\geq 35$  kg/m<sup>2</sup> or identify as Aboriginal and Torres Strait Islander, appropriately targeted subpopulations at high risk of diabetes-related complications. However, it was noted this still represented a very large eligible population.
- 7.4 With respect to the restriction, the PBAC noted that, consistent with the Committee's July 2023 advice, the pre-PBAC response accepted that one repeat would be appropriate for the 2.5 mg, 7.5 mg and 12.5 mg dose strengths of tirzepatide which are used for titration (paragraph 7.5, tirzepatide PSD, July 2023 PBAC Meeting). The PBAC considered the pre-PBAC response's proposal to allow use of tirzepatide in combination with a sulfonylurea was appropriate but reiterated its July 2023 advice that clinicians would also want to use tirzepatide in combination with insulin (paragraph 7.5, tirzepatide PSD, July 2023 PBAC Meeting). The PBAC considered the pre-PBAC response proposal to remove the continuation criteria based on glycaemic response was appropriate. The Committee also considered the pre-PBAC response proposed addition of a clinical criterion to the initiation treatment phase for patients treated with GLP-1 RA prior to the June 2024 restriction changes appropriate to ensure that these patients would not have to trial an SGLT2i prior to switching to tirzepatide treatment. As outlined in paragraph 7.2, the PBAC considered that restricting use to treatment by an endocrinologist, under the care of or in consultation with an endocrinologist as proposed in the pre-PBAC response, was not appropriate as

broader prescriber access is needed. The PBAC noted the resubmission request for an 'Authority Required – in writing' listing to mitigate the risk of use of tirzepatide in - people without diabetes. However, the PBAC also noted the ESC concerns that an 'Authority Required- in writing' listing would likely add an administrative burden to prescribers compared to the current GLP-1 RA prescribing.

- 7.5 The PBAC considered that the nomination of semaglutide as the main comparator was appropriate.
- 7.6 The PBAC noted that, as per the July 2023 submission, the SURPASS-2 trial was the key clinical trial with the resubmission providing new *post hoc* analyses of the trial including patients with a baseline BMI  $\geq 35$  kg/m<sup>2</sup>. The SURPASS-2 trial allowed comparison of tirzepatide 5 mg, 10 mg or 15 mg once weekly with semaglutide 1 mg once weekly. The PBAC did not accept the resubmission's claim that tirzepatide 5 mg would only be used as a temporary dose and hence a comparison of tirzepatide 5 mg versus semaglutide 1 mg was not relevant. Instead, the PBAC reaffirmed its July 2023 advice that this comparison was relevant given that 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 7.7, 7.11 tirzepatide PSD, July 2023 PBAC meeting). The PBAC recalled that in July 2023 it had considered that the data did not support superior efficacy of tirzepatide 5 mg versus semaglutide 1 mg (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). The PBAC noted that subgroup data in those with BMI  $\geq 35$  kg/m<sup>2</sup> were consistent with data in the whole trial population for this comparison. As such, the PBAC considered that superior efficacy was not supported for the comparison of tirzepatide 5 mg versus semaglutide 1 mg in this subgroup.
- 7.7 The resubmission described tirzepatide 10 mg or 15 mg once weekly as superior in terms of efficacy compared to semaglutide 1 mg once weekly based on the glycaemic benefits and short-term weight loss reported in the SURPASS-2 trial. The PBAC previously considered the claim was reasonable for the whole trial population (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). The PBAC considered the results in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> appeared consistent with results in the whole trial population. As such, the PBAC advised that the claim of superior comparative effectiveness was reasonable for tirzepatide 10 mg or 15 mg once weekly compared to semaglutide 1 mg once weekly in this subgroup.
- 7.8 The resubmission described tirzepatide 5 mg once weekly as superior in efficacy compared to semaglutide 0.5 mg once weekly based on the results of an indirect comparison using the SURPASS-2 trial and the SUSTAIN-7 trial. The PBAC recalled that it had previously considered this claim reasonable for the whole trial population (para 7.10, tirzepatide PSD, July 2023 PBAC meeting). The PBAC noted that while the point estimate favoured tirzepatide 5 mg compared to semaglutide 0.5 mg in the *post hoc* subgroup with BMI  $\geq 35$  kg/m<sup>2</sup>, in contrast to the whole trial population, the result did not achieve statistical significance or exceed the nominated MCID. However, the PBAC noted that results consistent with the whole trial population were evident with

respect to changes in mean body weight, with a numerically greater reduction in body weight based on the point estimate. Overall, the PBAC considered the claim of superior comparative efficacy for tirzepatide 5 mg once weekly compared to semaglutide 0.5 mg once weekly in the subgroup with BMI  $\geq 35$  kg/m<sup>2</sup> was uncertain but likely reasonable.

- 7.9 In terms of safety, the PBAC noted that the results based on the subgroup analysis of patients with BMI  $\geq 35$  kg/m<sup>2</sup> appeared similar to the whole trial population. As such, 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.
- 7.10 The PBAC noted the resubmission presented a modelled economic evaluation of tirzepatide 10 mg and 15 mg weekly compared to semaglutide 1 mg weekly, and the evaluation provided an additional analysis of tirzepatide 5 mg weekly versus semaglutide 1 mg weekly. The PBAC considered the additional analysis informative given the requested price for tirzepatide 5 mg was higher than semaglutide 1 mg.
- 7.11 The PBAC recalled that in July 2023 it had asked for any resubmission to include an economic model that addressed the Committee's concerns regarding circumstances of use (fixed dosing of GLP-1 RA/GIP and insulin therapies, perfect persistence, low threshold for insulin intensification (HbA1c > 7.5%) and no concomitant use of GLP-1 RA and insulin therapies) and weight-based utility/disutility (para 7.18 and para 7.13, tirzepatide PSD, July 2023 PBAC meeting). The PBAC recalled that it had advised a revised base case should incorporate: constant eGFR treatment effects; UKPDS drift for all biomarkers, insulin intensification at HbA1c 8.0% and reduced hypoglycaemia disutility to -0.003 per event (para 7.16, tirzepatide PSD, July 2023 PBAC meeting). The Committee had asked for a price reduction that results in an ICER in the order of \$30,000 per QALY gained (para 7.18, tirzepatide PSD, July 2023 PBAC meeting). The PBAC noted that the resubmission provided a revised base case model that addressed some but not all of the changes requested (see paragraph 6.67). The PBAC noted the revised base case model continued to assume that both tirzepatide and semaglutide are discontinued before switching to insulin therapy. The PBAC considered the ability to use semaglutide in combination with insulin is a key differentiating factor between the therapies (given that the proposed tirzepatide restriction specifically excludes combination therapy with insulin) with semaglutide frequently used in combination with insulin in clinical practice. The PBAC noted the impact on the ICER of correcting for this was uncertain as ongoing semaglutide would provide additional benefit at additional cost (see Table 11). In addition, the PBAC also noted the resubmission had increased the price of the highest maintenance dose and argued for a higher ICER based on targeting high risk populations.
- 7.12 The PBAC noted ESC advice that that the economic evaluation presented in the resubmission may not provide a basis for the PBAC to recommend tirzepatide for the proposed population with the ICER remaining uncertain. The PBAC noted that in response to the concerns raised by the ESC the pre-PBAC response provided a revised base case that included: switching to insulin/insulin intensification when HbA1c

> 7.5%; systolic blood pressure (SBP), heart rate and BMI remaining constant while on either tirzepatide or semaglutide with UKPDS biomarker drift applied while on insulin; and a price reduction for all doses of tirzepatide (see paragraph 3.2). The PBAC noted that the price of the highest maintenance dose remained higher than that proposed in July 2023. In addition, the PBAC noted the pre-PBAC response maintained that the proposed population are of sufficiently high unmet need to warrant an ICER of \$45,000 to < \$55,000 per QALY gained. The PBAC agreed with the ESC that the subgroup of patients with severe obesity is substantial and therefore does not justify the higher value proposition of a more targeted high risk group, such as Aboriginal and Torres Strait Islander peoples.

- 7.13 The PBAC noted that raising insulin initiation/intensification to HbA1c > 8.0% and applying UKPDS biomarker drift for all biomarkers in the pre-PBAC response model increased the ICERs for the comparison of tirzepatide 15 mg versus semaglutide 1 mg, tirzepatide 10 mg versus semaglutide 1 mg and tirzepatide 5 mg versus semaglutide 1 mg to \$55,000 to < \$75,000 per QALY, \$55,000 to < \$75,000 per QALY and \$115,000 to < \$135,000 per QALY respectively. The PBAC noted that the financial estimates assumed that ██████% of patients would receive the tirzepatide 5 mg dose (see Table 15). Overall, the PBAC considered the pre-PBAC response economic model did not adequately address the concerns raised by the Committee in July 2023 or the subsequent concerns raised by the ESC in this consideration with inadequate justification provided to refute the changes requested. The PBAC considered that the pre-PBAC response ICER was high and uncertain. Noting the modest price reductions provided in the pre-PBAC response, the PBAC advised that a revised economic model including a further price reduction would be required for the proposed listing to be considered cost-effective. The PBAC considered the revised base case inputs and considerations proposed by the ESC in paragraph 6.93 remained appropriate as the basis for revisions to the economic model. The PBAC also reaffirmed its July 2023 advice that an ICER in the order of \$30,000 per QALY would be appropriate.
- 7.14 Although the resubmission was targeted towards a narrower population than the July 2023 submission, the PBAC noted the estimated utilisation of tirzepatide and net cost to the PBS and RPBS presented in the resubmission were substantially higher than that seen previously. The PBAC noted the 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 the pre-PBAC response provided revised financial estimates which: changed the assumed duration of established eligibility of prevalent patients from 6 years to 3 years prior to the first PBS listing; adjusted the starting point for extrapolating the newly eligible incident population to October 2022; reduced the adherence rate from 100% to 93%; amended the persistence rate (see Table 15); and included the price reductions provided in the pre-PBAC response. The PBAC noted that no change to the uptake rate was made in the pre-PBAC response revised financial estimates and that despite amendments made the persistence estimates remained considerably higher than applied in the

economic model. The PBAC noted that the resulting net PBS/RPBS cost in the pre-PBAC response was 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 pre-PBAC response estimated utilisation and financial estimates were unable to be relied upon given they had not been evaluated.

- 7.15 The PBAC agreed with the 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.
- 7.16 The PBAC noted the pre-PBAC response identified the “opportunity cost of private market revenue” as a key consideration for the sponsor regarding the proposed PBS population, the proposed RSA and ultimately the price offered to Government for a PBS listing for T2DM.
- 7.17 The PBAC considered a resubmission for tirzepatide should address the following issues:
- Provide an economic model which incorporates the inputs and addresses the considerations raised by the ESC in paragraph 6.93 and a price reduction that results in an ICER in the order of \$30,000 per QALY; and
  - Provide revised financial estimates incorporating a revised price and addressing the issues outlined in 7.14.
  - Provide a revised RSA to address the high risk of use outside of the restriction.
  - Provide a revised restriction to address the PBAC recommendation regarding the restriction.

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

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

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about

other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.

## **10 Corrigendum**

The following changes were made:

<b>Change made</b>	<b>Date of revision</b>
Paragraph 6.109: Replaced "see paragraph 6.102" with "see paragraph 6.103"	11 April 2025
Paragraph 7.11: Replaced "see paragraph 6.66" with "see paragraph 6.67"	11 April 2025
Paragraph 7.13: Replaced "in paragraph 6.92" with "in paragraph 6.93"	11 April 2025
Paragraph 7.17: Replaced "in paragraph 6.92" with "in paragraph 6.93"	11 April 2025