

**5.14 TIRZEPATIDE,  
Injection 2.5 mg in 0.5 mL pre-filled pen,  
Injection 5 mg in 0.5 mL pre-filled pen,  
Injection 7.5 mg in 0.5 mL pre-filled pen,  
Injection 10 mg in 0.5 mL pre-filled pen,  
Injection 12.5 mg in 0.5 mL pre-filled pen,  
Injection 15 mg in 0.5 mL pre-filled pen,  
Mounjaro<sup>®</sup>,  
Eli Lilly Australia Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested an Authority Required (Telephone/Online) listing for tirzepatide for the treatment of adult patients with inadequately controlled type 2 diabetes as dual therapy in combination with metformin.
- 1.2 The submission claimed there remains a high unmet need for treatment alternatives that effectively address both glycaemic control and weight reduction, potentially mitigating the impact of disease progression and diabetes-related complications to the patient and broader society. The submission claimed tirzepatide offers superior effectiveness compared to existing treatment options, with a favourable safety and tolerability profile.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus current GLP-1 RA therapies (semaglutide, dulaglutide).

**Table 1: Key components of the clinical issue addressed in the submission**

Component	Description
Population	Patients with inadequately controlled type 2 diabetes, who meet specific prior therapy criteria <sup>a</sup>
Intervention	Tirzepatide 5 mg, 10 mg or 15 mg subcutaneous injection once weekly
Comparator	Main: Semaglutide 0.5 mg or 1.0 mg subcutaneous injection once weekly Secondary: Dulaglutide 1.5 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
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. Tirzepatide 5 mg, 10 mg or 15 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety when compared with dulaglutide 1.5 mg once weekly, when used in dual therapy with metformin.

Source: Table 1-1, p28 of the submission

<sup>a</sup> The target population in the submission was based on a draft restriction for GLP-1RAs in the DUSC Report 2023 (Attachment A8.14 of the submission). In March 2023, the PBAC recommended that the use of GLP-1 RAs should be restricted to patients who are contraindicated,



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Tirzepatide 7.5 mg/0.5 mL injection, vial	\$ <del> </del> published price \$ <del> </del> effective price	4	1	5	Mounjaro
Tirzepatide 10 mg/0.5 mL injection, vial	\$ <del> </del> published price \$ <del> </del> effective price	4	1	5	Mounjaro
Tirzepatide 12.5 mg/0.5 mL injection, vial	\$ <del> </del> published price \$ <del> </del> effective price	4	1	5	Mounjaro
Tirzepatide 15 mg/0.5 mL injection, vial	\$ <del> </del> published price \$ <del> </del> effective price	4	1	5	Mounjaro
<b>Category / Program:</b> General Schedule					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Administrative Advice:</b> Special Pricing Arrangements Apply [TBC]					
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333					
<b>Condition:</b> Diabetes mellitus Type 2					
<b>Indication:</b> Diabetes mellitus Type 2					
<b>Clinical criteria:</b>					
The treatment must be combination therapy limited to: (i) metformin, and (ii) a glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist (GIP/GLP-1 RA);					
<b>AND</b>					
<b>Clinical criteria:</b>					
The condition must be inadequately responsive to either (i) metformin, (ii) a sulfonylurea, or (iii) insulin, but only where treatment with metformin is not possible					
<b>AND</b>					
<b>Clinical criteria:</b>					
- The patient must have a contraindication/intolerance requiring permanent treatment discontinuation to an SGLT2 inhibitor; OR - The condition must be/have been inadequately responsive to combination treatment with a SGLT2 inhibitor plus metformin; OR - The condition must be/have been inadequately responsive to combination treatment with a sulfonylurea plus metformin; OR - The condition must be/have been inadequately responsive to combination treatment with insulin plus metformin (or insulin alone where the patient is contraindicated/intolerant to metformin); OR - Patient must have a contraindication/intolerance requiring permanent treatment discontinuation to combination therapy with metformin plus a sulfonylurea with GLP-1 receptor agonist treatment commenced prior to [insert date of change here]					
<b>Clinical criteria:</b>					
The treatment must not be prescribed in combination with either: (i) a SGLT2 inhibitor, (ii) a DPP4 inhibitor, (iii) pioglitazone, (iv) another GLP-1 receptor agonist					

**Prescribing Instructions:**

**Definition:**

A HbA1c measurement greater than 7% despite treatment with the specified prior therapy/therapies indicates inadequate responsiveness.

Where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period indicates inadequate responsiveness.

Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies:

- (a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies),
- (b) Red cell transfusion within the previous 3 months.

Document HbA1c measurements (blood glucose measurements where relevant), as well as any intolerances/contraindications in the patient's medical records.

- 3.2 The submission requested PBS-listings for both the prefilled pen and vial presentations of tirzepatide, however only the pre-filled pen can be considered in this submission (see paragraph 2.2 above).
- 3.3 The submission did not adequately justify the need for 5 repeats for the 2.5 mg, 7.5 mg and 12.5 mg dose strengths. The product information recommends a minimum treatment duration of 4 weeks at these strengths, for titration purposes only. The ESC considered that one repeat would be reasonable for these dose strengths.
- 3.4 The submission requested a special pricing arrangement consisting of the following rebates on the published DPMQ: |% for 2.5 mg and 5 mg strengths, |% for 7.5 mg and 10 mg strengths and |% for the 12.5 mg and 15 mg strengths. This results in flat pricing across the different strengths. The submission noted that special pricing arrangements are currently in place for semaglutide and dulaglutide.
- 3.5 The proposed restrictions for dual therapy with tirzepatide were modelled on the draft restriction for GLP-1 RAs in the DUSC 2023 report. In March 2023, the PBAC recommended that the use of GLP-1 RAs in all type 2 diabetes indications should be restricted to patients who are contraindicated, intolerant or inadequately responsive to SGLT2 inhibitors (PBAC outcomes, March 2023 PBAC meeting). However, at that time the PBAC noted that further consultation will be conducted on the wording of the restriction. The ESC noted that the outcome of the post March 2023 meeting consultation is not yet known and advised that the wording of the proposed tirzepatide restriction may require revision once the consultation is finalised.
- 3.6 The proposed tirzepatide restriction was narrower than intended for GLP-1 RAs as it does not allow for use of tirzepatide in combination with sulfonylurea or insulin.
- 3.7 No justification was provided for not allowing combination use of tirzepatide with sulfonylurea. There are published data for the use of tirzepatide versus insulin glargine with mixed background therapies of metformin ± sulfonylurea (SURPASS-AP-Combo) and metformin ± sulfonylurea ± SGLT2 inhibitors (SURPASS-4) that were not included in the submission.

- 3.8 The submission claimed that historically, listings of combinations with insulin have been assessed separately, therefore combination use of tirzepatide with insulin was not proposed in the current submission. There are published data for tirzepatide as add-on therapy to metformin and insulin glargine versus placebo (SURPASS-5 trial) that were not included in the submission.
- 3.9 The ESC questioned whether it was clinically appropriate to exclude combination use of tirzepatide with sulfonylurea or insulin given the available clinical data (SURPASS-4, SURPASS-5, SURPASS-AP-Combo) and the likely combination use in clinical practice.

*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, in both men and women with increasing age, Aboriginal and Torres Strait Islanders 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 Treatment guidelines recommend a step-wise approach to the management of type 2 diabetes with two main goals; cardiorenal risk reduction in high-risk patients, and achievement and maintenance of glycaemic control and weight management. Metformin is currently recommended as the first-line pharmacological therapy while the choice of additional therapies should be guided by the presence of comorbidities (cardiovascular disease, heart failure, chronic kidney disease and obesity), side effect profiles and cost. Guidelines note a preference for GLP-1 RA therapies in patients with cardiovascular disease or obesity and a preference for SGLT2 inhibitors in patients with heart failure or chronic kidney disease. Guidelines also recommend the combined use of GLP-1 RA therapies and SGLT2 inhibitors if patients are unable to achieve treatment targets. Patients unable to maintain glycaemic control may also initiate insulin therapy. The guidelines consider that sulfonylureas and DPP4 inhibitors have a more limited role in the management of type 2 diabetes (ADA/EASD 2022; ADS 2022).
- 4.4 The Australian guidelines also note the PBS status of therapies and therefore specifically prioritise SGLT2 inhibitors over GLP-1 RA therapies and note that

combination use of SGLT2 inhibitors and GLP-1 RA therapies is not subsidised on the PBS (ADS 2022). As noted above in paragraph 3.5, there will be further consultation on the PBS restriction wording following the March 2023 PBAC outcome of the review of PBS restrictions for type 2 diabetes. It was acknowledged by PBAC that it would be important in this consultation process to note that PBS restrictions may differ from clinical guidelines due to the consideration of the cost-effectiveness of comparator treatments (PBAC outcomes, March 2023 PBAC meeting).

- 4.5 Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide regulates blood glucose by stimulating insulin secretion, increasing insulin sensitivity, reducing glucagon secretion and delaying gastric emptying. The exact mechanism by which tirzepatide reduces body weight is unclear but is thought to be related to lower energy intake due to an overall reduction in appetite. The GIP component is thought to act primarily through enhancing the GLP-1 receptor mediated effects.
- 4.6 Tirzepatide is self-administered as a subcutaneous injection. Available doses are 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg. The starting dose is 2.5 mg once weekly for 4 weeks, increasing to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after at least 4 weeks on the current dose. The recommended doses are 5 mg, 10 mg and 15 mg once weekly. The product information states that 2.5 mg, 7.5 mg and 12.5 mg once weekly are not maintenance doses.

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

## **5 Comparator**

- 5.1 The submission nominated semaglutide as the main comparator and dulaglutide as a secondary comparator. The main arguments provided in support of this nomination were similarities in mechanism of action (targeting GLP-1 receptor), as well as the method and frequency of administration (once weekly injection). The submission also claimed that semaglutide has the largest market share within the GLP-1 RA market and therefore would be the therapy most likely to be replaced. The ESC considered the nominated comparators were appropriate.
- 5.2 The submission claimed that both semaglutide and tirzepatide exhibit a dose-response relationship in terms of efficacy and gastrointestinal adverse events, therefore only tirzepatide 10 mg and 15 mg would be considered suitable alternatives to semaglutide 1 mg. No data were presented in support of this assumption. The direct comparison of tirzepatide 5 mg versus semaglutide 1 mg in the SURPASS-2 trial was also considered relevant during the evaluation.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (7) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals described the effects of type 2 diabetes on quality of life and described hope that tirzepatide treatment will improve symptoms and weight loss.
- 6.3 Input from health care professionals described a range of benefits of treatment with tirzepatide including weight loss, a potential reduction in cardiovascular / cardiovascular associated events, and reduced glycated haemoglobin (HbA1c) indicating better glucose control. The health care professional input described gastrointestinal adverse effects, such as nausea and vomiting. The disadvantages of injections were noted but health care professional input indicated the frequency and self-administration of tirzepatide injections generally made treatment manageable for individuals. The input from health care professionals also described the lack of access to tirzepatide due to cost, prescription complexities and supply shortages.
- 6.4 The three organisations that provided input were Western Sydney Diabetes, Western Sydney Local Health District (WSLHD), Diabetes Australia and National Aboriginal Community Controlled Health Organisation (NACCHO). Input from Western Sydney Diabetes, WSLDH, described how a major part of type 2 diabetes management is blood sugar control, weight loss and protecting against complications, especially in the heart and kidney. The input described the benefits of tirzepatide in terms of the management of diabetes, obesity and the co-morbidities associated with these conditions. The input from Western Sydney diabetes highlighted the GIP function is new and working with GLP-1 is a substantial improvement in diabetes management but noted that upper gastric symptoms will limit use by some people.
- 6.5 Diabetes Australia described access to medications and treatments to manage type 2 diabetes as essential to ensuring people live well with the condition and reduce their risk of developing debilitating and costly diabetes complications. The input also highlighted that the ongoing shortage of semaglutide indicates the importance of having multiple therapeutic options for Australians living with difficult to manage type 2 diabetes.
- 6.6 Input from NACCHO highlighted that diabetes prevalence is 2.9 times as high among Indigenous Australians as non-Indigenous Australians and noted that Aboriginal and Torres Strait Islander peoples are 4.2 times more likely to be hospitalised, and 4.9 times more likely to die from diabetes. The NACCHO input requested that GLP1 injections and tirzepatide be included on the PBS list for Aboriginal and Torres Strait

Islander peoples under a Streamline Authority for those with type 2 diabetes or pre-diabetes with obesity with no further restrictions. Given poverty, poor food supply in remote areas, and the very high rates of kidney disease (also some of the fastest progression of kidney disease in the world) and heart disease, the NACCHO input stated that there is a justification for enhanced access to these drugs for Aboriginal people, without some of the current PBS restrictions and/or for use in obesity without diabetes on the PBS.

### **Clinical trials**

6.7 The submission was based on the following comparisons:

- Direct comparison of tirzepatide 10 mg and 15 mg versus semaglutide 1.0 mg in patients on background metformin therapy (SURPASS-2).
- Supportive indirect comparison of tirzepatide 5 mg (SURPASS-2) versus semaglutide 0.5 mg (SUSTAIN 7) with semaglutide 1.0 mg as the common reference in patients on background metformin therapy.
- Supportive indirect comparison of tirzepatide 5 mg, 10 mg and 15 mg (SURPASS-2) versus dulaglutide 1.5 mg (SUSTAIN 7) with semaglutide 1.0 mg as the common reference in patients on background metformin therapy.

6.8 The direct comparison of tirzepatide 5 mg versus semaglutide 1.0 mg in the SURPASS-2 trial was also considered relevant during the evaluation.

6.9 There were a number of other trials of tirzepatide for type 2 diabetes that were not included in the submission; multiple studies assessing glycaemic control and weight management compared to different comparators (SURPASS-1, SURPASS-3, SURPASS-4, SURPASS-5, SURPASS-J MONO, SURPASS-J COMBO), a cardiovascular outcomes trial (SURPASS-CVOT, expected completion October 2024), a paediatric study (SURPASS-PEDS, expected completion December 2027) and two GLP-1 RA switching studies (SURPASS-SWITCH and SURPASS-SWITCH2, expected completion July 2024 and October 2023 respectively).

6.10 Details of the trials presented in the submission are provided in Table 2.

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

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
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

Source: Table 2(a).2.1, p71; Attachments A1.1-1.4 of the submission

6.11 The key features of the included trials are summarised in Table 3.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<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	Used to inform 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	Used to inform treatment effects for semaglutide 0.5 mg and dulaglutide

Source: Section 2(a).4, pp80-90; Section 2(b).4, pp161-173 of the submission

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

- 6.12 The open-label design of the SURPASS-2 and SUSTAIN 7 trials has the potential to introduce bias as knowledge of treatment assignment may affect disease management decisions (particularly the use of concomitant medications), patient expectations and treatment adherence. As well as the open-label design of the SURPASS-2 trial, the ESC noted that publication of the key trial<sup>1</sup> indicated the authors of the trial publication were employed by the sponsor. The ESC agreed with the evaluator that the risk of bias with the SURPASS-2 trial was high.
- 6.13 There was differential discontinuation between arms in the SURPASS-2 trial (tirzepatide 5 mg 8.3%, tirzepatide 10 mg 12.4%, tirzepatide 15 mg 13.2%, semaglutide 1.0 mg 8.7%), primarily due to higher rates of gastrointestinal adverse events in the higher dose tirzepatide arms.
- 6.14 Patients included in the clinical trials were required to have inadequate glycaemic control despite treatment with metformin alone. The ESC noted that the SURPASS-2 trial excluded patients treated with any antihyperglycaemic medication other than metformin in the 3 months prior to study commencement, which may not be representative of the proposed PBS population. In addition, the population may not be representative of the revised place in therapy for GLP-1 RA therapies that was proposed in the draft PBS restrictions which limits use to patients failing prior therapy with SGLT2 inhibitors (para 5.15, PBS restrictions for type 2 diabetes mellitus medicines, March 2023 PBAC meeting).
- 6.15 The trials used fixed dosing of tirzepatide and semaglutide which was inconsistent with the respective product information documents which recommend flexible titration of both therapies.

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<sup>1</sup> Frias JP, Davies M, Rosenstock J et al. Tirzepatide versus semaglutide once weekly in patients with Type 2 diabetes. *NEJM* 2021; 385:503-15.

## Comparative effectiveness

6.16 The change in HbA1c from baseline to Week 40 in the SURPASS-2 trial is summarised in Table 4. The reported estimates in the main trial publication (Frias 2021) and those considered by regulatory agencies were based on the treatment regimen estimand which used data from the full in-trial period with multiple imputation for missing data based on retrieved dropouts who had an endpoint value (i.e. equivalent to an ITT analysis).

**Table 4: Change in HbA1c from baseline to Week 40 (treatment regimen estimand)**

HbA1c, %	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 469	Semaglutide 1 mg N = 468
Baseline, mean (SD)	8.32 (1.08)	8.30 (1.02)	8.26 (1.00)	8.25 (1.01)
Week 40, mean (SD)	6.23 (0.98)	5.99 (0.97)	5.92 (0.97)	6.37 (0.98)
Change from baseline, LSM (SE)	-2.01 (0.04)	-2.24 (0.05)	-2.30 (0.05)	-1.86 (0.05)
Tirzepatide vs semaglutide, LSM difference (95% CI)	<b>-0.15 (-0.28, -0.03)</b>	<b>-0.39 (-0.51, -0.26)</b>	<b>-0.45 (-0.57, -0.32)</b>	-

Source: Table 2(a).5.1, p92 of the submission

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

Note: Bolded estimates indicate statistically significant results based on graphical testing results controlled for Type I error

6.17 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.

6.18 Analyses of results based on the efficacy estimand (data censored for patients who discontinued treatment or received rescue therapy) were consistently more favourable for tirzepatide compared to semaglutide (see below).

**Table 5: Change in HbA1c from baseline: efficacy estimand**

	Mean difference
tirzepatide 5 mg vs semaglutide 0.5 mg *	<b>-0.53 (-0.74, -0.32)</b>
tirzepatide 5 mg vs semaglutide 1 mg ^	<b>-0.23 (-0.36, -0.10)</b>
tirzepatide 10 mg vs semaglutide 1 mg ^	<b>-0.51 (-0.64, -0.38)</b>
tirzepatide 15 mg vs semaglutide 1 mg ^	<b>-0.60 (-0.73, -0.47)</b>

Source: Submission, Table 2(a).5.1, p92; PSCR

\* indirect comparison; ^ head-to-head comparison

6.19 Subgroup analyses of HbA1c results indicated that race and baseline BMI may be potential treatment effect modifiers.

6.20 The submission claimed the results demonstrated superiority for all three doses of tirzepatide compared to semaglutide. The results met the primary outcome of non-inferiority and secondary outcome of superiority in terms of statistical significance. However, the point estimates for the treatment regimen estimand did not exceed the submission's nominated minimal clinically important difference (MCID) of 0.5 percentage points. The submission claimed the PBAC has previously considered a 0.5 percentage point reduction in HbA1c as a potential MCID for testing superiority

(semaglutide Public Summary Document (PSD), November 2019 and March 2021 PBAC meetings). The clinical importance of the magnitude of reduction in HbA1c is uncertain given the changing treatment algorithms based on more patient-centred outcomes. The ESC considered the claim of superiority for all three doses of tirzepatide was supported by statistical significance but questioned whether the superior benefit in HbA1c was clinically meaningful given the MCID had not been met for the mean differences based on the treatment regimen estimand presented in the evaluation. The ESC noted that efficacy estimand analyses presented in the submission and PSCR involve causal inference and complex statistics but may be considered a legitimate approach<sup>2</sup>. The pre-PBAC response noted that using the efficacy estimates (see Table 5 above), the HbA1c mean differences of tirzepatide 10 mg or 15 mg compared to semaglutide 1 mg could be considered clinically meaningful based on an MCID of 0.5 percentage points reduction

- 6.21 The proportions of patients achieving HbA1c targets of < 7.0%, ≤ 6.5% and < 5.7% at 40 weeks in the SURPASS-2 trial are presented in Table 6. The reported estimates were based on the treatment regimen estimand.

**Table 6: Proportion of patients achieving HbA1c targets at Week 40 (treatment regimen estimand)**

HbA1c, %	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 469	Semaglutide 1 mg N = 468
<b>&lt;7.0%</b>				
Patients, n (%)	385 (82.0)	401 (85.6)	404 (86.2)	370 (79.0)
Tirzepatide vs semaglutide, OR (95% CI)	1.29 (0.91, 1.83)	<b>1.68 (1.15, 2.45)</b>	<b>1.72 (1.18, 2.51)</b>	-
<b>≤6.5%</b>				
Patients, n (%)	323 (68.8)	362 (77.1)	374 (79.7)	298 (63.6)
Tirzepatide vs semaglutide, OR (95% CI)	1.34 (1.00, 1.79)	2.06 (1.53, 2.84)	2.40 (1.75, 3.30)	-
<b>&lt;5.7%</b>				
Patients, n (%)	128 (27.1)	187 (39.8)	214 (45.7)	88 (18.9)
Tirzepatide vs semaglutide, OR (95% CI)	1.72 (1.25, 2.38)	<b>3.20 (2.33, 4.38)</b>	<b>4.11 (3.01, 5.63)</b>	-

Source: Table 2(a).5.2, p92 of the submission

Abbreviations: CI, confidence interval; OR, odds ratio

Note: Bolded estimates indicate statistically significant results based on graphical testing results controlled for Type I error

- 6.22 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, although the ≤6.5% target was unadjusted for multiplicity. There were no statistically significant differences between tirzepatide 5 mg and semaglutide after adjustment for multiplicity.

<sup>2</sup> ICH Harmonised Guideline, November 2019, Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1): [https://database.ich.org/sites/default/files/E9-R1\\_Step4\\_Guideline\\_2019\\_1203.pdf](https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf)

6.23 The change in body weight from baseline to Week 40 in the SURPASS-2 trial is summarised in Table 7. The reported estimates were based on the treatment regimen estimand.

**Table 7: Change in body weight at 40 weeks (treatment regimen estimand)**

Body weight, kg	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 469	Semaglutide 1 mg N = 468
Baseline, mean (SD)	92.5 (21.8)	94.8 (22.7)	93.8 (21.8)	93.7 (21.1)
Week 40, mean (SD)	84.5 (21.0)	85.3 (22.3)	82.3 (20.0)	87.7 (20.4)
Change from baseline, LSM (SE)	-7.6 (0.33)	-9.3 (0.32)	-11.2 (0.32)	-5.7 (0.32)
Tirzepatide vs semaglutide, LSM difference (95% CI)	<b>-1.9 (-2.8, -1.0)</b>	<b>-3.6 (-4.5, -2.7)</b>	<b>-5.5 (-6.4, -4.6)</b>	-

Source: Table 2(a).5.3, p97 of the submission

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

Note: Bolded estimates indicate statistically significant results based on graphical testing results controlled for Type I error

6.24 Treatment with tirzepatide 5 mg, 10 mg and 15 mg was associated with statistically significant reductions in body weight at Week 40, with treatment differences of between -1.9 to -5.5 kg compared to semaglutide 1 mg. The magnitude of effect increased with increasing tirzepatide dose.

6.25 Analyses of results based on the efficacy estimand (data censored for patients who discontinued treatment or received rescue therapy) were more favourable for tirzepatide 10 and tirzepatide 15 mg but were less favourable for tirzepatide 5 mg compared to semaglutide.

6.26 Subgroup analyses of body weight results indicated that age, baseline BMI, duration of diabetes, geographic region and ethnicity may be potential treatment effect modifiers.

6.27 The submission claimed that the treatment differences for tirzepatide 10 mg and 15 mg versus semaglutide 1 mg were clinically important, with point estimates exceeding the nominated MCID of 3 kg. The quantification of the impact of weight loss on the risk of downstream complications remains highly uncertain. The PBAC has previously raised concerns regarding the lack of long-term data supporting reductions in downstream complications for treatments claiming weight loss benefits (semaglutide for obesity PSD, March 2022 PBAC meeting; semaglutide for type 2 diabetes PSD, November 2019 PBAC meeting; exenatide PSDs, July 2007 and November 2008 PBAC meetings; sibutramine PSDs, November 2006 and March 2008 PBAC meetings).

6.28 The proportions of patients achieving a 5%, 10% or 15% reduction in body weight at 40 weeks in the SURPASS-2 trial are presented in Table 8. The reported estimates were based on the treatment regimen estimand.

**Table 8: Proportion of patients achieving weight loss targets at Week 40 (treatment regimen estimand)**

Weight loss target	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 469	Semaglutide 1 mg N = 468
<b>≥5%</b>				
Patients, n (%)	307 (65.3)	357 (76.2)	374 (79.7)	253 (54.0)
Tirzepatide vs semaglutide, OR (95% CI)	1.62 (1.23, 2.14)	2.81 (2.09, 3.79)	3.43 (2.53, 4.64)	-
<b>≥10%</b>				
Patients, n (%)	162 (34.5)	219 (46.7)	267 (56.9)	112 (23.9)
Tirzepatide vs semaglutide, OR (95% CI)	1.69 (1.26, 2.27)	2.89 (2.16, 3.85)	4.32 (3.24, 5.77)	-
<b>≥15%</b>				
Patients, n (%)	69 (14.7)	112 (23.9)	168 (35.8)	37 (8.0)
Tirzepatide vs semaglutide, OR (95% CI)	2.00 (1.31, 3.06)	3.73 (2.50, 5.57)	6.66 (4.51, 9.82)	-

Source: Table 2(a).5.1, p92 of the submission

Abbreviations: CI, confidence interval; OR, odds ratio

- 6.29 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.
- 6.30 Treatment with tirzepatide was also associated with some nominal improvements in blood pressure and lipid parameters compared to semaglutide.
- 6.31 The change in quality-of-life measures (using generic: EQ VAS, EQ-5D-5L and weight specific instruments: IWQOL-Lite-CT) from baseline to Week 40 in the SURPASS-2 trial are summarised in Table 9.

**Table 9: Change in quality-of-life measures at 40 weeks (full analysis set)**

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
<b>EQ VAS<sup>a</sup></b>				
Baseline, mean (SD)	74.4 (18.0)	74.7 (15.9)	75.8 (17.6)	74.8 (16.8)
Week 40, mean (SD)	82.7 (14.4)	83.6 (13.4)	83.3 (15.2)	82.3 (14.6)
Change from baseline, LSM (SE)	7.8 (0.6)	8.6 (0.6)	8.0 (0.6)	7.3 (0.6)
Tirzepatide vs semaglutide, LSM difference (95% CI)	0.4 (-1.3, 2.1)	1.3 (-0.4, 3.0)	0.7 (-1.0, 2.4)	-
<b>EQ-5D-5L (UK index)<sup>b</sup></b>				
Baseline, mean (SD)	0.82 (0.22)	0.82 (0.19)	0.82 (0.20)	0.81 (0.20)
Week 40, mean (SD)	0.85 (0.19)	0.86 (0.19)	0.85 (0.20)	0.85 (0.20)
Change from baseline, LSM (SE)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.03 (0.01)
Tirzepatide vs semaglutide, LSM difference (95% CI)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	-
<b>IWQOL-Lite-CT (Total score)<sup>c</sup></b>				
Baseline, mean (SD)	69.8 (22.5)	68.7 (22.6)	67.8 (23.7)	71.2 (21.5)
Week 40, mean (SD)	78.8 (17.7)	78.2 (18.8)	78.5 (18.9)	77.8 (19.0)
Change from baseline, LSM (SE)	9.0 (0.7)	9.0 (0.7)	9.9 (0.7)	7.3 (0.7)
Tirzepatide vs semaglutide, LSM difference (95% CI)	1.7 (-0.2, 3.5)	1.7 (-0.1, 3.5)	2.6 (0.7, 4.4)	-
<b>IWQOL-Lite-CT (Physical composite subscore)</b>				
Baseline, mean (SD)	65.4 (23.8)	63.6 (24.8)	63.3 (25.1)	66.5 (23.3)
Week 40, mean (SD)	74.7 (20.7)	73.7 (23.0)	74.3 (22.4)	72.9 (22.2)
Change from baseline, LSM (SE)	9.4 (0.8)	9.5 (0.8)	10.4 (0.8)	7.0 (0.8)
Tirzepatide vs semaglutide, LSM difference (95% CI)	2.3 (0.2, 4.5)	2.4 (0.3, 4.6)	3.4 (1.2, 5.5)	-
<b>IWQOL-Lite-CT (Psychosocial composite subscore)</b>				
Baseline, mean (SD)	72.1 (24.3)	71.5 (24.2)	70.1 (25.5)	73.7 (23.0)
Week 40, mean (SD)	81.0 (18.7)	80.5 (19.2)	80.6 (19.8)	80.4 (19.7)
Change from baseline, LSM (SE)	8.8 (0.7)	8.8 (0.7)	9.6 (0.7)	7.5 (0.7)
Tirzepatide vs semaglutide, LSM difference (95% CI)	1.3 (-0.7, 3.2)	1.3 (-0.7, 3.3)	2.1 (0.2, 4.1)	-

Source: Table GPG.L.8.61, p1568; Table GPG.L.8.63, p1706 of the SURPASS-2 trial report

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

<sup>a</sup> EQ VAS scores range from 0 to 100, higher scores indicate better quality of life

<sup>b</sup> EQ-5D-5L UK index scores range from -0.285 to 1, higher scores indicate better quality of life

<sup>c</sup> IWQOL-Lite-CT Total scores range from 0 to 100, higher scores indicate better weight-related quality of life

<sup>d</sup> IWQOL-Lite-CT Physical composite scores range from 0 to 100, higher scores indicate better weight-related quality of life specific to physical impacts due to weight

<sup>e</sup> IWQOL-Lite-CT Psychosocial composite scores range from 0 to 100, higher scores indicate better weight-related quality of life specific to emotional and social impacts due to weight

6.32 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).

6.33 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 1.0 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.

- 6.34 The quality-of-life results were consistent with other patient-reported outcomes (Impact of Weight on Self-Perceptions Questionnaire; Diabetes Treatment Satisfaction Questionnaire; Ability to Perform Physical Activities of Daily Living) which indicated minimal differences between treatment arms.
- 6.35 Based on the supportive indirect comparison of tirzepatide 5 mg (SURPASS-2) versus semaglutide 0.5 mg (SUSTAIN 7), treatment with tirzepatide 5 mg was associated with a statistically significant reduction in HbA1c (mean difference -0.53 percentage points; 95% CI 0.74, -0.32) and body weight (mean difference -3.5 kg; 95% CI -4.70, -2.30) compared to semaglutide 0.5 mg.
- 6.36 Based on the supportive indirect comparison of tirzepatide 5 mg, 10 mg and 15 mg (SURPASS-2) versus dulaglutide 1.5 mg (SUSTAIN 7)<sup>3</sup>:
- treatment with tirzepatide 5 mg was associated with a statistically significant reduction in HbA1c (mean difference -0.63 percentage points; 95% CI -0.84, -0.42) and body weight (mean difference -5.1 kg; 95% CI -6.29, -3.91) compared to dulaglutide 1.5 mg.
  - treatment with tirzepatide 10 mg was associated with a statistically significant reduction in HbA1c (mean difference -0.91 percentage points; 95% CI -1.12, -0.70) and body weight (mean difference -7.6 kg; 95% CI -8.80, -6.40) compared to dulaglutide 1.5 mg.
  - treatment with tirzepatide 15 mg was associated with a statistically significant reduction in HbA1c (mean difference -1.00 percentage points; 95% CI -1.21, -0.79) and body weight (mean difference -9.7 kg; 95% CI -10.90, -8.50) compared to dulaglutide 1.5 mg.

### **Comparative harms**

- 6.37 Table 10 presents an overall summary of the adverse events reported with tirzepatide and semaglutide treatment in the SURPASS-2 trial.

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<sup>3</sup> Note that the results presented in Paragraph 6.36 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 and SUSTAIN-7. 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.

Table 10: Summary of key adverse events in the SURPASS-2 trial

Patients, n (%)	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1.0 mg N=469
Any adverse event	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)
Treatment-related adverse event	188 (40.0)	221 (47.1)	225 (47.9)	194 (41.4)
Serious adverse event	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)
Adverse events leading to treatment discontinuation	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)
Adverse events leading to study discontinuation	5 (1.1)	8 (1.7)	5 (1.1)	4 (0.9)
Deaths	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)
<b>Adverse events of special interest</b>				
Gastrointestinal events	188 (40.0)	216 (46.1)	211 (44.9)	193 (41.2)
Hypoglycaemia <sup>a</sup>	3 (0.6)	1 (0.2)	8 (1.7)	2 (0.4)
Severe hypoglycaemia	1 (0.2)	0	1 (0.2)	0
Injection site reaction	9 (1.9)	13 (2.8)	21 (4.5)	1 (0.2)
Adjudicated pancreatitis	0	2 (0.4)	2 (0.4)	3 (0.6)
Cholelithiasis	4 (0.9)	4 (0.9)	4 (0.9)	2 (0.4)
Hypersensitivity	9 (1.9)	13 (2.8)	8 (1.7)	11 (2.3)
Diabetic retinopathy	0	2 (0.4)	0	0

Source: Table 2(a).5.1, p104 of the submission; Table 2, Frias 2021 publication; Table GPG.L5.27, SURPASS-2 trial report

<sup>a</sup> Clinically significant, defined as blood glucose level <3 mmol/L or severe hypoglycaemia

- 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.
- 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 The submission stated that indirect comparisons of safety between the SURPASS-2 trial and SUSTAIN 7 trial were unreliable due to substantial differences in the reported incidence of events in the common comparator arm.
- 6.42 The submission provided additional data on potential safety concerns with tirzepatide based on a Periodic Safety Update Report (May 2022 to November 2022). The report

includes use of tirzepatide 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg for type 2 diabetes, overweight/obesity, non-alcoholic steatohepatitis and heart failure with preserved ejection fraction. There was limited post-marketing exposure as tirzepatide was first authorised for type 2 diabetes in the US in May 2022, with subsequent authorisations globally including the EU and Japan.

- 6.43 Hypersensitivity was identified as a new adverse drug reaction for tirzepatide. There were no important identified risks. Important potential risks include medullary thyroid cancer, pancreatic malignancy, diabetic retinopathy complications, gallbladder disorders, hypotension, dizziness and hair loss. The report identified missing information in regard to pregnancy and lactation.
- 6.44 Overall, there are limited data to support the long-term safety of tirzepatide given the limited duration of exposure for most patients (< 1 year).

### **Benefits/harms**

- 6.45 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 5 mg in comparison with semaglutide 1 mg over 40 weeks:
- There would be no additional patients achieving conventional glycaemic targets (< 7.0%) or glycaemic normalisation (< 5.7%).
  - 11 additional patients would experience  $\geq 5\%$  weight loss, 11 additional patients would experience  $\geq 10\%$  weight loss and 7 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 measures and patient reported outcomes.
  - There would be one fewer patient with gastrointestinal events (e.g. nausea, vomiting, diarrhoea) and no difference in patients with hypoglycaemia.
- 6.46 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 10 mg in comparison with semaglutide 1 mg over 40 weeks:
- There would be 7 additional patients achieving conventional glycaemic targets (< 7.0%) and 21 additional patients achieving glycaemic normalisation (< 5.7%).
  - 22 additional patients would experience  $\geq 5\%$  weight loss, 23 additional patients would experience  $\geq 10\%$  weight loss and 16 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 measures and patient reported outcomes.
  - There would be 5 additional patients with gastrointestinal events (e.g. nausea, vomiting, diarrhoea) and no difference in patients with hypoglycaemia.
- 6.47 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 15 mg in comparison with semaglutide 1 mg over 40 weeks:

- There would be 7 additional patients achieving conventional glycaemic targets (< 7.0%) and 27 additional patients achieving glycaemic normalisation (< 5.7%).
- 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 measures and patient reported outcomes.
- There would be 4 additional patients with gastrointestinal events (e.g. nausea, vomiting, diarrhoea) and 2 additional patients with hypoglycaemia.

### **Clinical claim**

- 6.48 The submission described tirzepatide 5 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to semaglutide 0.5 mg once weekly. The evaluation concluded this efficacy claim was reasonable in terms of a statistically significant change in HbA1c and weight loss which exceeded the nominated MCIDs for both outcomes. The claim of non-inferior safety was not adequately supported.
- 6.49 The submission did not make a clinical claim for tirzepatide 5 mg once weekly versus semaglutide 1 mg once weekly. Based on data presented in the submission, tirzepatide 5 mg appeared similar in terms of efficacy (did not meet the nominated MCIDs for either HbA1c or weight loss) and potentially similar or inferior in terms of safety. The PSCR objected to the comparisons of tirzepatide 5 mg versus semaglutide 1 mg presented in the evaluation. The PSCR argued that this was inappropriate as it compared low-dose tirzepatide with high-dose semaglutide and that it was more reasonable to low dose tirzepatide (5 mg) with low dose semaglutide (0.5 mg). However, the ESC considered that the relative efficacy and safety (and subsequently cost-effectiveness) of tirzepatide 5 mg compared to semaglutide 1 mg was relevant given that submission requested a higher price for low dose tirzepatide compared to high dose semaglutide (see paragraph 6.58).
- 6.50 The submission described tirzepatide 10 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to semaglutide 1 mg once weekly. The evaluation concluded this efficacy claim was reasonable in terms of a statistically significant change in HbA1c and weight loss, with the difference based on the treatment regimen estimand exceeding the nominated MCID for weight but not HbA1c. The claim of non-inferior safety was not adequately supported.
- 6.51 The submission described tirzepatide 15 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to semaglutide 1 mg once weekly. The evaluation concluded this efficacy claim was reasonable in terms of a statistically significant change in HbA1c and weight loss, with the difference based on the treatment regimen estimand exceeding the nominated MCID for weight but not HbA1c. The claim of non-inferior safety was not adequately supported.

- 6.52 The submission described tirzepatide 5 mg, 10 mg and 15 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to dulaglutide 1.5 mg once weekly. The evaluation concluded this efficacy claim was reasonable in terms of a statistically significant change in HbA1c and weight loss which exceeded the nominated MCIDs for both outcomes. The claim of non-inferior safety was not adequately supported.
- 6.53 The evaluation considered the following issues should be considered:
- There were multiple evidence gaps in the clinical data; including a lack of data for flexible dose titration, limited long term efficacy data (maximum 40 weeks) particularly regarding cardiovascular outcomes as well as limited long-term safety data (typically < 1 year exposure across the broader tirzepatide clinical program). The PSCR argued that the fixed dose titration regimen is common in clinical trials of type 2 diabetes medicines even when a flexible dose titration regimen is used in clinical practice (semaglutide PSD, November 2019). In addition, the PSCR argued that there is precedent for the PBAC recommending the listing of alternative antihyperglycemic medicines based on trials with shorter trial durations (semaglutide PSD, March 2021, linagliptin + metformin PSD, March 2016). However, the ESC noted the PBAC had not recommended these medicines based on superiority claims.
  - The clinical claim of superiority was based on HbA1c and weight loss benefits. The PBAC previously considered the clinical relevance of change in HbA1c may shift in the context of changing treatment algorithms based on patient-centred outcomes (para 7.5, semaglutide PSD, November 2019 PBAC meeting). The PBAC has also raised concerns regarding the lack of long-term data supporting reductions in downstream complications for treatments claiming weight loss benefits (semaglutide for obesity PSD, March 2022 PBAC meeting; semaglutide for type 2 diabetes PSD, November 2019 PBAC meeting). The PSCR argued that UK Prospective Diabetes Study has clearly shown an association between HbA1c improvement and a reduction in macro- and micro-vascular outcomes (Stratton et al, 2000) and that the PBAC has recommended other antihyperglycemic medicines based on HbA1c prior to the availability of cardiovascular outcomes. However, the ESC noted the PBAC had not recommended these medicines based on superiority claims.
  - Tirzepatide 5 mg, 10 mg and 15 mg once weekly was potentially inferior in terms of safety compared to semaglutide 1 mg once weekly, due to higher incidence of gastrointestinal adverse events including serious adverse events and adverse events leading to discontinuation. Results from the key trial showed a dose-dependent increase in the risk of gastrointestinal adverse events with tirzepatide. The PSCR argued that the forced titration regimen may have influenced the frequency of adverse events (see paragraph 6.39). In addition, the PSCR noted that the SURPASS-2 study was not designed as a non-inferiority study for safety outcomes and argued there was no clear evidence of a dose-dependent

relationship between tirzepatide and severe adverse events. The ESC considered the PSCR claim that inflexible dose titration may lead to greater risk of experiencing adverse events may be reasonable but advised that this would also apply to semaglutide. The pre-PBAC response noted that the number of titration steps (each 4 weeks) differs between the medicines to reach the maximum dose (tirzepatide 5 titration steps versus semaglutide 2 titration steps). As such, the pre-PBAC response argued that the safety comparison is biased against tirzepatide based on the inflexible dose titration in the clinical trials compared to the flexible dosing that occurs in practice.

- 6.54 The ESC considered that the claim of superior clinical efficacy for tirzepatide 5 mg once weekly compared to semaglutide 0.5 mg once weekly was supported, but the comparison of tirzepatide 5 mg and semaglutide 1 mg remained relevant given the proposed higher pricing relative to semaglutide 1 mg. This comparison did not support a clinically meaningful difference. The ESC also advised the claim of superior efficacy for tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly compared to semaglutide 1 mg once weekly was reasonable and clinically meaningful if using the efficacy estimand but inadequately supported based on the treatment regimen estimand, which is the analysis used in the key trial publication.
- 6.55 The ESC agreed with the evaluation that a non-inferior safety claim was not adequately supported for any of the comparisons.
- 6.56 The PBAC considered 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 agreed with the ESC that the comparison of tirzepatide 5 mg and semaglutide 1 mg remained relevant, but this comparison did not support a clinically meaningful difference.
- 6.57 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data for any of the comparisons.

### ***Economic analysis***

- 6.58 The submission presented a modelled economic evaluation of tirzepatide 10 mg and 15 mg weekly compared to semaglutide 1 mg weekly based on clinical data from the SURPASS-2 trial with additional modelled data. During the evaluation, an additional comparison of tirzepatide 5 mg weekly versus semaglutide 1 mg weekly (based on the SURPASS-2 trial) was presented given the lack of an established dose equivalency between treatments and the use of flat pricing structures which results in a higher price for tirzepatide 5 mg weekly compared to semaglutide 1 mg weekly. The ESC considered this additional analysis was informative.
- 6.59 The submission also presented a scenario analysis comparing tirzepatide 5 mg weekly with semaglutide 0.5 mg weekly based on an indirect comparison of the SURPASS-2 and SUSTAIN-7 trials with additional modelled data. Scenario analyses were also

presented comparing tirzepatide 5 mg, 10 mg and 15 mg weekly with dulaglutide 1.5 mg weekly based on another indirect comparison of the SURPASS-2 and SUSTAIN-7 trials with additional modelled data.

6.60 All economic evaluations were presented as a cost-effectiveness/cost-utility analysis.

**Table 11: 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)
Methods used to generate results	Patient-level microsimulation model (10,000 patients; runtime approximately 30-40 minutes).
Treatments	Tirzepatide (10 mg or 15 mg weekly) or semaglutide (1 mg weekly) in combination with metformin with two further lines of insulin intensification therapy (basal insulin, basal and bolus insulin).
Model structure	<p>The model tracked individual patient-level changes in surrogate biomarkers over time.</p> <p>The risk of events in each annual cycle was 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 were also used to capture treatment-specific event rates for hypoglycaemia and nausea.</p> <p>The risk of death was 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>
Cycle length	1 year (no half cycle correction)
Patient characteristics and circumstances of use	<p>Baseline age, gender, race, smoking status, duration of diabetes, HbA1c, systolic blood pressure, LDL, HDL, BMI, eGFR, heart rate 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 population. Baseline white blood cell counts and haemoglobin levels were estimated based on the derivation cohort of the UKPDS study (Hayes 2013).</p> <p>The submission 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 HbA1c &gt; 7.5% and would intensify treatment if the same threshold was reached again, assumed GLP-1 RA/GIP therapy must be stopped with the initiation of insulin, assumed flat dosing of insulin therapies.</p>
Transition probabilities	<p>Treatment effects for GLP-1RA/GIP therapy were based on the SURPASS-2 trial. The submission sampled treatment effects for individual modelled patients assuming a normal distribution around mean values. Changes to biomarkers were assumed to remain constant over time while on therapy with the exception of HbA1c which was assumed to gradually increase over time based on the UKPDS OM2 risk equations. No modelled patients were allowed to discontinue prematurely.</p> <p>Patients were assumed to intensify therapy with insulin when HbA1c &gt; 7.5%. Insulin intensification was assumed to revert all biomarkers (except HbA1c) to baseline values. Insulin treatment effects on HbA1c were estimated based on a systematic review of insulin studies (Willis 2017).</p> <p>Adverse event risk for GLP-1RA/GIP therapy was estimated based on the SURPASS-2 trial. 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. The risk of death was based on UKPDS OM2 risk equations for 'first year of events' and 'subsequent years of events' as</p>

Component	Description
	well as Australian life tables for 'years with no event history or events' and 'years with history of events but no events'.
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 &amp; 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 58 years or older.</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 &amp; 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 flat effective DPMQ. The cost of semaglutide was based on fixed dosing of 1 mg per week and the effective DPMQ (as this was known to the sponsor). The costs of metformin, insulin glargine and insulin aspart were based on WHO defined daily doses and 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 submission 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 submission 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> <p>Diabetes complications costs were primarily based on panel data from Western Australia using linked administrative claims databases (Clarke 2008). The submission inflated costs using the CPI health index.</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Section 3.2-3.6, pp264-295 of the submission

Abbreviations: BMI, body mass index; CPI, consumer price index; DPMQ, dispensed price per maximum quantity; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic peptide; GLP-1 RA glucagon-like peptide-1 receptor agonists; HbA1c, HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; UKPDS (OM2), United Kingdom Prospective Diabetes Study (Outcomes Model 2); WHO, World Health Organization

- 6.61 A set of baseline characteristics (demographics, biomarkers, history of complications) is individually generated for each modelled patient. Over the course of the model, all patients experience disease progression characterised by a gradual increase in HbA1c over time.
- 6.62 The model incorporates treatment effects for each therapy based on changes to HbA1c, systolic blood pressure, LDL cholesterol, HDL cholesterol, body mass index, estimated glomerular filtration rate and heart rate.
- 6.63 Patients are initially treated with GLP-1 RA/GIP therapies until their HbA1c levels increase to 7.5% 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 7.5% 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.

- 6.64 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.
- 6.65 The risks of diabetes complications and mortality vary over time based on current biomarkers, demographic characteristics and prior event history.
- 6.66 During the evaluation, an error was noted in the calculation of both basal and bolus insulin costs as the submission incorrectly assumed 1,500 IU were dispensed per prescription (based on 5 pens) rather than 7,500 IU per prescription (based on 5 packs of 5 pens). This error was corrected during the evaluation.
- 6.67 The price of insulin aspart was subject to a mandatory price reduction on 1 April 2023 which decreased the price from \$211.62 per script (used in the submission) to \$166.22 per script. The updated price was used during the evaluation.
- 6.68 During the evaluation an inconsistency was noted in the application of treatment effects for eGFR with some parts of the submission stating that estimates revert to baseline in the second-line setting (model structure, risk factor progression, treatment effects) while alternatively eGFR remained constant at the level observed with first line therapy (event simulation). Similar inconsistencies were also noted in model spreadsheet. During the evaluation, the base case analysis was respecified assuming eGFR reverts to baseline for all treatment arms to maintain consistency between analyses. The PSCR claimed that the assumption that eGFR remains unchanged upon insulin intensification was appropriate as increases on treatment discontinuation would imply that renal function is restored. The ESC acknowledged the PSCR argument and noted the effect on the ICER of allowing first-line treatment effects for eGFR while receiving later lines of therapy was negligible (see Table 14).
- 6.69 Key drivers of the economic model are summarised in Table 12.

**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Circumstances of use	The modelled circumstances of use were based on the following assumptions: - Flat dosing of both tirzepatide (5 mg, 10 mg, 15 mg weekly) and semaglutide (1 mg weekly). This assumption was consistent with the trial data but was unlikely to reflect use in clinical practice as both PIs recommend flexible dose titration. - Patients cannot prematurely discontinue therapy. This assumption was inconsistent with the SURPASS-2 trial data which indicated that 8.3% of tirzepatide 5 mg, 12.4% of tirzepatide 10 mg, 13.2% of tirzepatide 15 mg and 8.7% of semaglutide 1 mg patients discontinued therapy over the 40-week trial duration. In clinical practice, patients will discontinue therapy for a variety of reasons.	High, direction unclear

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Description	Method/Value	Impact
	<ul style="list-style-type: none"> <li>- Patients would switch to insulin therapy if HbA1c levels exceed the treatment target of 7.5%. The submission assumed that insulin therapy would be intensified if patients reached the same threshold again. This assumption may not be appropriate as the ESC has previously advised the PBAC that HbA1c levels are often greater than 8% before switching to insulin in clinical practice (para 6.76, semaglutide PSD, November 2019 PBAC meeting). The PSCR argued that a threshold of 7.5% is consistent with that outlined in the PBS restrictions for use of medicines in combination with insulin. The ESC reaffirmed its previous advice that a HbA1c threshold of at least 8% would be more reflective of current clinical practice.</li> <li>- Patients must stop tirzepatide and semaglutide before switching to insulin therapy. The ESC agreed with the evaluation that this assumption was inappropriate for semaglutide given that both the current and draft PBS restriction for semaglutide allow concomitant therapy with insulin. In practice, it is likely that GLP-1 RA treatments would be continued in combination with insulin due to their established glycaemic control and weight loss benefits. The ESC also considered there would likely be continued use of tirzepatide alongside insulin given clinical data in this setting (SURPASS-5) and potential weight gain with insulin. The pre-PBAC response noted that SURPASS-5 was conducted in patients who are insufficiently controlled on insulin glargine and subsequently have tirzepatide added to their treatment regimen. The pre-PBAC response argued that inclusion of concomitant use of a GLP-1 RA/GIP and insulin therapies in the economic model would require evidence on a different treatment sequence, namely, patients inadequately controlled on tirzepatide or a GLP-1 RA having insulin added to their regimen. The pre-PBAC response stated that such evidence was not available.</li> <li>- Flat dosing of insulin therapies (basal insulin 40 IU/day; basal with bolus insulin 80 IU/day). This assumption was not consistent with use of insulin in clinical practice as therapy is typically titrated over time to maintain glycaemic control.</li> </ul>	
<p>Biomarker change over time</p>	<p>The submission estimated the drift in HbA1c values over time based on the United Kingdom Prospective Diabetes Study Outcome Model 2 (UKPDS OM2) risk equation. This equation used 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 this equation 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 may be appropriate to calibrate the equation against more contemporary datasets (such as GLP-1 RA cardiovascular outcome studies).</p> <p>The submission assumed no drift for other biomarkers (e.g. systolic blood pressure, LDL cholesterol, HDL cholesterol, body mass index, estimated glomerular filtration rate, heart rate, white blood cell counts, haemoglobin). The submission claimed that this assumption was likely to be conservative given that tirzepatide was generally associated with more favourable treatment effects on these biomarkers compared to semaglutide. The ESC considered this assumption was not clinically appropriate and agreed with the evaluation that this claim was not adequately supported given that sensitivity analyses conducted during the evaluation indicated that incorporating drift in other biomarkers into the model substantially worsened the estimated cost-effectiveness of tirzepatide compared to semaglutide. The pre-PBAC response stated that by only considering HbA1c progression over time the long-term treatment effect of both tirzepatide and semaglutide was isolated. The pre-PBAC response argued this provided a more relevant comparative assessment of the clinical and</p>	<p>High, favours tirzepatide</p>

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Description	Method/Value	Impact
	economic impacts of improved glycaemic control on micro- and macrovascular complications.	
GLP-1 RA/GIP treatment effects	<p>The submission estimated the treatment effects for both tirzepatide and semaglutide based on the SURPASS-2 trial. The estimates used in the model were primarily based on results using the efficacy estimand. The submission did not adequately justify the use of the efficacy estimand versus the treatment-regimen estimand in the economic analysis. Sensitivity analyses indicated that the relative cost-effectiveness of tirzepatide 5 mg compared to semaglutide 1 mg substantially improved while the cost-effectiveness of tirzepatide 10 mg and 15 worsened when treatment-regimen estimand data was used in the model.</p> <p>With the exception of HbA1c, the submission assumed all other treatment effects associated with GLP-1 RA/GIP therapy will cease when patients switch to insulin and discontinue their initial therapy. The submission did not adequately justify the assumption that HbA1c levels would remain unaffected by patients stopping GLP-1 RA/GIP therapy.</p>	High, direction unclear
Weight-related disutility/utility values	<p>The submission estimated first year utility gains associated with weight loss based on a vignette study using time trade-off valuation of hypothetical health states to assess the impact of weight loss in obese patients with or without type 2 diabetes in the United Kingdom (Boye 2022). The estimates used in the submission were based on the reported values for obese patients with type 2 diabetes. The submission 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 trial. The submission did not justify applying utility estimates to population-level data rather than modelled individual estimates of weight change. Additionally, the model did not include any disutility for weight gain during the first year. The approach used in the submission resulted in implausible scenarios such as patients with modelled weight gain also accruing the utility benefits associated with substantial weight loss.</p> <p>The submission estimated the disutility associated with weight in subsequent years based on a cross-sectional survey of 4,641 type 2 diabetes patients recruited from European centres in 1998 using the EQ-5D-3L questionnaire (CODE-2 study; Bagust &amp; Beale, 2005). This source was not adequately justified, given the submission acknowledged that there are a 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 submission 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 submission 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. 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.</p> <p>The ESC considered the disutility associated with weight gain was overestimated (see paragraphs 6.70 to 6.72).</p>	High, direction unclear
Hypoglycaemia event rates	<p>Hypoglycaemia event rates for tirzepatide and semaglutide were based on the reported event rates for clinically significant hypoglycaemia in the SURPASS-2 trial.</p> <p>The submission estimated hypoglycaemia event rates associated with insulin treatment (both second and third-line therapy) based on a multinational, observational study of diabetes patients switching from existing insulin therapies to</p>	High, favours tirzepatide

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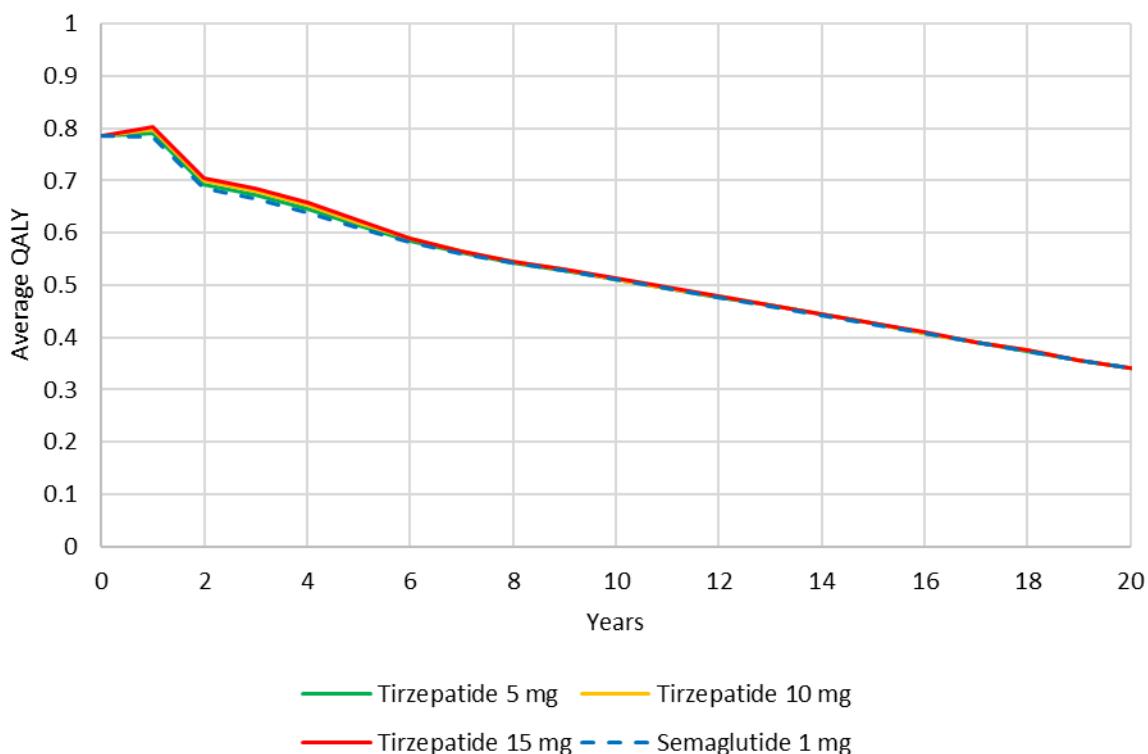
Description	Method/Value	Impact
	<p>insulin degludec between March 2015 and March 2018 (Fadini 2019). The applicability of this study to the modelled population was unclear as the publication acknowledged that the inclusion criteria limited enrolment to patients with a pre-planned switch to insulin degludec, which may have selected a population with frequent hypoglycaemia (56.6% of the type 2 diabetes population in the study were classified as hypoglycaemia-prone patients).</p> <p>The definition of hypoglycaemia for insulin (an event with or without symptoms which was either confirmed or assumed to be caused by blood glucose &lt; 3.9 mmol/L) was inconsistent with the definition used to inform event rates for tirzepatide and semaglutide (a severe event requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose &lt; 3.0 mmol/L). This difference in definition is likely to substantially overestimate the relative hypoglycaemia event rate with insulin compared to tirzepatide and semaglutide (1,400 versus 0.47-2.12 per 100 patient years). The PSCR acknowledged that the difference in definitions will lead to a higher event rate for insulin but argued that the impact was likely to be relatively minor as once patients have had insulin intensified in both arms, event rates are equivalent. The ESC considered the assumption of 14 hypoglycaemic episodes per year for insulin treatment was not clinically plausible. The ESC noted that lower hypoglycaemia rates were reported in the SURPASS-4 trial (which used the same definitions as the SURPASS-2 trial) with the impact on the ICER explored in a sensitivity analysis (see Table 14).</p>	

Source: Constructed during the evaluation

Abbreviations: BMI, body mass index; GIP, glucose-dependent insulinotropic peptide; GLP-1 RA glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; IU, international units; PBAC, Pharmaceutical Benefits Advisory Committee; PI, product information; PSD, Public Summary document; UKPDS (OM2), United Kingdom Prospective Diabetes Study (Outcomes Model 2)

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

Figure 1: Markov trace of average undiscounted QALYs over time



Source: Constructed during the evaluation based on tirzepatide Section 3 model Excel spreadsheet

Abbreviations: QALY, quality adjusted life year

Note: Markov trace was truncated to 20 years.

- 6.71 The modelled changes in average QALYs after one year of treatment (tirzepatide 5 mg: +0.005, 10 mg: +0.013; 15 mg: +0.017; semaglutide 1 mg: -0.001) were inconsistent with the available utility data from the SURPASS-2 trial (all treatment arms: +0.04). The submission did not address the lack of internal consistency between modelled and observed utility data.
- 6.72 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. The PSCR stated that a weight change utility was applied in the first year and a BMI level utility was applied in all subsequent years when body weight was assumed to be stable. As such, the PSCR claimed there was no double-counting of utility impacts given the utilities were applied at different times and to different aspects of body weight, i.e. year 1 change in body weight; subsequent years living with a BMI ≥ 25 kg/m<sup>2</sup>. The ESC advised that whilst it was reasonable to have utility changes based on weight alone, the approach taken by the submission was flawed. Firstly, the decrement from year 2

onwards for a BMI  $\geq 25$  kg/m<sup>2</sup> does not account for the potential improvement in utility for patients having significant weight loss from baseline, even if BMI remains over 25 kg/m<sup>2</sup>. Secondly, double-counting occurs with the use of utility inputs from Boye et al 2022 and separate addition of decrements for diabetes complications. The ESC advised that the source of the year 1 change in body weight utilities (time trade-off data from Boye et al 2022) doesn't control for diabetes complications and hence does not isolate the weight loss effect. The ESC observed that the Bagust and Beale 2005 study used as the basis for weight-related disutility in subsequent years did control for diabetes complications, however given the first issue identified above, altering the first-year utilities would not address lack of internal consistency between modelled and observed utilities as the model results in substantial QALY losses in all arms after the first year of treatment despite the substantial weight loss observed in all arms. In addition, the ESC noted that Bagust and Beale 2005 reported decrements for complications lower than those based on Clarke 2002, which was used as the source of baseline utility and disutility values (Table 11).

- 6.73 The ESC noted that a flat rate disutility value of 0.005 sourced from Evans 2013 was applied per non-severe daytime hypoglycaemic episode. The ESC advised that this lacked face validity as the Evans 2013 data showed a diminishing disutility per event as the number of events increases. The use of the flat rate for the decrement in utility associated with hypoglycaemia was significant because once patients move onto insulin treatment, they were assumed to experience 14 hypoglycaemic episodes per year. The sensitivity analysis showed that the model was sensitive to the disutility applied for hypoglycaemia, with the ICER per QALY changing close to 50% with removal of the hypoglycaemia disutility (see Table 14). The ESC noted that the Evans 2013 data suggests monthly events leads to a reduction in utility of 0.003 per event and considered this may be a better estimate than the 0.005 used by the submission. The ESC did not consider this number of hypoglycaemic events once on insulin treatment was clinically plausible.
- 6.74 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 7 years.
- 6.75 The results of the modelled economic evaluation using effective prices are summarised in Table 13.

Table 13: Results of the modelled economic evaluation

Type of resource item	Tirzepatide	Semaglutide	Incremental difference
<b>Comparison of tirzepatide 5 mg versus semaglutide 1 mg</b>			
Costs	\$	\$	\$
LYs	13.2404	13.2283	0.0121
QALYs	8.4517	8.4121	0.0396
<b>Incremental cost per LY gained</b>			\$ <sup>1</sup>
<b>Incremental cost per QALY gained</b>			\$ <sup>2</sup>
<b>Comparison of tirzepatide 10 mg versus semaglutide 1 mg</b>			
Costs	\$	\$	\$
LYs	13.2494	13.2283	0.0211
QALYs	8.4987	8.4121	0.0866
<b>Incremental cost per LY gained</b>			\$ <sup>3</sup>
<b>Incremental cost per QALY gained</b>			\$ <sup>4</sup>
<b>Comparison of tirzepatide 15 mg versus semaglutide 1 mg</b>			
Costs	\$	\$	\$
LYs	13.2566	13.2283	0.0283
QALYs	8.5264	8.4121	0.1143
<b>Incremental cost per LY gained</b>			\$ <sup>5</sup>
<b>Incremental cost per QALY gained</b>			\$ <sup>6</sup>

Source: Table 3.8-2, p300 of the submission

Abbreviations: LY, life year; QALY, quality-adjusted life year

Note: The submission incorrectly estimated insulin drug costs based on 1500 IU per script rather than 7500 IU per script. This error was corrected during the evaluation.

Note: The price of insulin aspart was subject to a mandatory price reduction on 1 April 2023 which decreased the price from \$211.62 per script (used in the submission) to \$166.22 per script (used in the evaluation).

Note: During the evaluation an inconsistency was noted in the estimation of treatment effects for eGFR with insulin intensification. In order to address the inconsistency, the base case analyses were respecified during the evaluation by assuming that eGFR reverts to baseline for all treatment arms.

The redacted values correspond to the following ranges:

<sup>1</sup> \$355,000 to < \$455,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$255,000 to < \$355,000

<sup>4</sup> \$55,000 to < \$75,000

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

<sup>6</sup> \$45,000 to < \$55,000

6.76 Based on the economic model, treatment with tirzepatide was associated with an incremental cost per QALY gained of \$115,000 to < \$135,000 for the 5 mg dose, \$55,000 to < \$75,000 for the 10 mg dose (uncorrected estimate: \$35,000 to < \$45,000) and \$45,000 to < \$55,000 for the 15 mg dose (uncorrected estimate: \$25,000 to < \$35,000) compared to semaglutide 1 mg weekly. The ESC considered that the ICERs per QALY were high, particularly for those based on lower doses, and all ICERs were likely under-estimated due to optimistic assumptions, particularly around utility weights and insulin intensification (see Table 12 for the values used). In addition, the ESC considered the large variation between the ICER for the 5 mg dose and the ICERs reported for the higher doses of tirzepatide indicates that a flat pricing structure (which results in a higher price for tirzepatide 5 mg weekly compared to semaglutide 1 mg weekly) may not be appropriate.

6.77 Scenario analyses indicated that treatment with tirzepatide 5 mg compared to semaglutide 0.5 mg weekly was associated with an incremental cost per QALY gained

of \$55,000 to < \$75,000 (uncorrected estimate: \$45,000 to < \$55,000). Scenario analyses also indicated that treatment with tirzepatide was associated with an incremental cost per QALY gained of \$35,000 to < \$45,000 for the 5 mg dose (uncorrected estimate: \$25,000 to < \$35,000), \$25,000 to < \$35,000 for the 10 mg dose (uncorrected estimate: \$15,000 to < \$25,000) and \$25,000 to < \$35,000 (uncorrected estimate: \$5,000 to < \$15,000) for the 15 mg dose compared to dulaglutide 1.5 mg weekly.

- 6.78 The submission identified the tirzepatide 15 mg dose uncorrected ICER of \$25,000 to < \$35,000 as the base case and claimed that the PBAC has previously accepted an ICER range of \$25,000 to \$35,000 per QALY gained as cost-effective for diabetes treatments (DUSC report 2023, PBS restrictions for type 2 diabetes mellitus medicines, Paragraph 2.4). The referenced statement was noting the ICER range from the SGLT2 inhibitor report and did not indicate that the PBAC had accepted this range as cost-effective. At that time, the PBAC recommended a further price reduction for SGLT2 inhibitors based on forecast total expenditure (DUSC report 2023, PBS restrictions for type 2 diabetes mellitus medicines, Paragraph 2.5).
- 6.79 For every 10,000 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 (24 fewer non-fatal events) and an increase in survival (average gain of 9 days per patient).
  - Decreased incidence of patients with nausea in the first year (50 fewer patients).
  - Improved quality of life associated with a temporary reduction in weight (average increase of 0.0153 quality-adjusted life years).
  - Delayed time to insulin therapy (average 2.64 months per patient) with a reduced incidence of hypoglycaemia events (27,220 fewer events).
  - Additional drug and administration costs of \$1 million but decreased diabetes complication costs of \$0.2 million.
- 6.80 For every 10,000 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 (54 fewer non-fatal events) and an increase in survival (average gain of 17 days per patient).
  - Increased incidence of patients with nausea in the first year (130 additional patients).
  - Improved quality of life associated with a temporary reduction in weight (average increase of 0.0402 quality-adjusted life years).
  - Delayed time to insulin therapy (average 5.88 months per patient) with a reduced incidence of hypoglycaemia events (61,273 fewer events).

- Additional drug and administration costs of \$1 million but decreased diabetes complication costs of \$0.5 million.

6.81 For every 10,000 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 (77 fewer non-fatal events) and an increase in survival (average gain of 23 days per patient).
- Increased incidence of patients with nausea in the first year (420 additional patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0570 quality-adjusted life years).
- Delayed time to insulin therapy (average 6.84 months per patient) with a reduced incidence of hypoglycaemia events (70,502 fewer events).
- Additional drug and administration costs of \$1 million but decreased diabetes complication costs of \$2.2 million.

6.82 The results of key sensitivity analyses are summarised in Table 14.

**Table 14: 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>	\$1	\$6	\$7
<b>Discount rate (base case: 5% for benefits and costs)</b>			
3.5% discount rate	\$1 <sup>1</sup> (-4%)	\$6 <sup>6</sup> (-4%)	\$7 <sup>7</sup> (-4%)
0% discount rate	\$2 <sup>2</sup> (-15%)	\$7 <sup>7</sup> (-15%)	\$11 <sup>11</sup> (-17%)
<b>Biomarker drift (base case: HbA1c drift based on UKPDS OM2 equation; no drift for other biomarkers)</b>			
No drift for any biomarker	\$3 <sup>3</sup> (+15%)	\$5 <sup>5</sup> (+23%)	\$6 <sup>6</sup> (+28%)
UKPDS drift for all biomarkers	\$4 <sup>4</sup> (+22%)	\$5 <sup>5</sup> (+27%)	\$6 <sup>6</sup> (+32%)
<b>GLP1-RA/GIP treatment effects (base case: tirzepatide and semaglutide treatments effects based on efficacy estimands with standard deviations back-calculated from the SURPASS 2 trial)</b>			
Remove HbA1c treatment effects for both arms but retain all other treatment effects	\$4 <sup>4</sup> (+79%)	\$1 <sup>1</sup> (+89%)	\$5 <sup>5</sup> (+97%)
Use lower CI for mean difference in HbA1c	\$2 <sup>2</sup> (-22%)	\$6 <sup>6</sup> (-11%)	\$11 <sup>11</sup> (-7%)
Use upper CI for mean difference in HbA1c	\$4 <sup>4</sup> (+49%)	\$6 <sup>6</sup> (+14%)	\$7 <sup>7</sup> (+12%)
Allow constant first-line treatment effects for eGFR while receiving later lines of therapy	\$1 <sup>1</sup> (-3%)	\$6 <sup>6</sup> (-2%)	\$7 <sup>7</sup> (-1%)
Remove BMI treatment effects for both arms but retain all other treatment effects	\$4 <sup>4</sup> (+40%)	\$2 <sup>2</sup> (+53%)	\$5 <sup>5</sup> (+71%)
Use lower CI for mean difference in BMI	\$1 <sup>1</sup> (-13%)	\$6 <sup>6</sup> (-4%)	\$7 <sup>7</sup> (-3%)
Use upper CI for mean difference in BMI	\$3 <sup>3</sup> (+10%)	\$6 <sup>6</sup> (+4%)	\$7 <sup>7</sup> (+7%)

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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>	\$ <sup>1</sup>	\$ <sup>6</sup>	\$ <sup>7</sup>
Use treatment-regimen estimands for biomarkers reported in Valentine 2023 for SURPASS-2 trial	\$ <sup>5</sup> (-38%)	\$ <sup>6</sup> (+15%)	\$ <sup>6</sup> (+20%)
<b>Insulin treatment (base case: insulin intensification steps when HbA1c &gt; 7.5%; insulin dose 40 IU/day second-line and 80 IU third-line, treatment effects for HbA1c and BMI based on Willis 2017; hypoglycaemia rates based on Fadini 2019)</b>			
Insulin intensification at HbA1c 8.0%	\$ <sup>4</sup> (+31%)	\$ <sup>5</sup> (+19%)	\$ <sup>6</sup> (+19%)
Insulin intensification at HbA1c 8.5%	\$ <sup>4</sup> (+44%)	\$ <sup>5</sup> (+47%)	\$ <sup>6</sup> (+47%)
Reduce insulin hypoglycaemia rate to 400 per 100 patient years (severe or BG confirmed episodes from Fadini 2019)	\$ <sup>4</sup> (+30%)	\$ <sup>5</sup> (+30%)	\$ <sup>6</sup> (+26%)
Reduce insulin hypoglycaemia rate to 23 per 100 patient years (based on the SURPASS-4 trial) <sup>a</sup>	\$ <sup>4</sup> (+46%)	\$ <sup>5</sup> (+47%)	\$ <sup>6</sup> (+39%)
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>6</sup> savings per QALY foregone (NE)	\$ <sup>5</sup> savings per QALY foregone (NE)	\$ <sup>1</sup> savings per QALY foregone (NE)
<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 &amp; Beale 2005)</b>			
Hypoglycaemia disutility removed	\$ <sup>4</sup> (+47%)	\$ <sup>5</sup> (+48%)	\$ <sup>6</sup> (+40%)
Reduce hypoglycaemia disutility to -0.003 per event	\$ <sup>3</sup> (+15%)	\$ <sup>6</sup> (+15%)	\$ <sup>7</sup> (+13%)
Weight-related utility/disutility removed	\$ <sup>4</sup> (+64%)	\$ <sup>2</sup> (+80%)	\$ <sup>5</sup> (+91%)
Subsequent weight disutility based on Soloft 2009	\$ <sup>4</sup> (+23%)	\$ <sup>5</sup> (+30%)	\$ <sup>6</sup> (+34%)
Subsequent weight disutility based on Lane 2014	\$ <sup>7</sup> (-60%)	\$ <sup>10</sup> (-65%)	\$ <sup>10</sup> (-67%)
<b>Multivariate analysis</b>			
Scenario 1: Constant eGFR treatment effects, UKPDS drift for all biomarkers, insulin intensification at HbA1c 8.0%, reduced hypoglycaemia event rate based on SURPASS-4	\$ <sup>8</sup> (+332%)	\$ <sup>4</sup> (+183%)	\$ <sup>1</sup> (+171%)
Scenario 2: Constant eGFR treatment effects, UKPDS drift for all biomarkers, insulin intensification at HbA1c 8.0%, reduced hypoglycaemia disutility to -0.003 per event	\$ <sup>9</sup> (+151%)	\$ <sup>1</sup> (+96%)	\$ <sup>5</sup> (+96%)

Source: Table 3.9-2, pp305-306 of the submission; additional analyses conducted during the evaluation based on tirzepatide Section 3 model Excel spreadsheet

Abbreviations: BMI, body mass index; GLP-1 RA glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; ICER, incremental cost effectiveness ratio; NE, not estimated; QALY, quality-adjusted life year; UKPDS (OM2), United Kingdom Prospective Diabetes Study (Outcomes Model 2)

Note: The submission incorrectly estimated insulin drug costs based on 1500 IU per script rather than 7500 IU per script. This error was corrected during the evaluation.

Note: The price of insulin aspart was subject to a mandatory price reduction on 1 April 2023 which decreased the price from \$211.62 per script (used in the submission) to \$166.22 per script (used in the evaluation).

Note: During the evaluation an inconsistency was noted in the estimation of treatment effects for eGFR with insulin intensification. In order to address the inconsistency, the base case analyses were respecified during the evaluation by assuming that eGFR reverts to baseline for all treatment arms

<sup>a</sup> Based on rate per year in patients without sulfonylurea in the SURPASS-4 trial using the same definition of 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)

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$95,000 to < \$115,000

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

<sup>4</sup> \$155,000 to < \$255,000

<sup>5</sup> \$75,000 to < \$95,000

<sup>6</sup> \$55,000 to < \$75,000

<sup>7</sup> \$45,000 to < \$55,000

<sup>8</sup> \$555,000 to < \$655,000

<sup>9</sup> \$255,000 to < \$355,000

<sup>10</sup> \$15,000 to < \$25,000

<sup>11</sup> \$35,000 to < \$45,000

6.83 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).

6.84 The ESC noted the results of the sensitivity analyses indicated that the model was most sensitive to biomarker drift factors, HbA1c and BMI treatment effects, insulin intensification thresholds, hypoglycaemia rates with insulin, hypoglycaemia and weight-related utility values as well as the use of concomitant semaglutide with insulin. The ESC considered that optimistic assumptions around utility weights, biomarker drift and insulin intensification should be addressed by revised base case that incorporated:

- Constant eGFR treatment effects
- UKPDS drift for all biomarkers
- Insulin intensification at HbA1c 8.0%
- Reduced hypoglycaemia disutility to -0.003 per event.

The ESC noted that this increased the base case ICER from \$115,000 to < \$135,000 to \$255,000 to < \$355,000 per QALY gained for the 5 mg dose, from \$55,000 to < \$75,000 to \$115,000 to < \$135,000 per QALY gained for the 10 mg dose and from \$45,000 to < \$55,000 to \$75,000 to < \$95,000 per QALY gained for the 15 mg dose. As outlined in paragraph 6.72, the ESC considered that the use of utility inputs from Boye et al 2022 was not appropriate and advised that amendment would further increase the ICER but could not be done within the existing model.

6.85 The ESC advised against considering a weighted ICER approach as there is no strong basis to determine weights for each dose strength (the estimates presented in the submission were based on assumptions). It should be noted that, while the submission considered the 15 mg would be the most widely used option, the TGA delegate considered that this dose would only be used in a minority of patients.

**Drug cost/patient/year**

6.86 The submission proposed a flat pricing structure for all dose strengths of tirzepatide (2.5, 5, 7.5, 10, 12.5 and 15 mg). The estimated drug cost for tirzepatide per patient per year was \$| (based on the effective DPMQ per script \$| / 28 days per script x 365.25 days per year).

6.87 The estimated drug cost for semaglutide per patient per year was \$█ (based on the effective DPMQ per script \$| / 28 days per script x 365.25 days per year).

**Table 15: Drug cost per patient for tirzepatide**

	<b>SURPASS-2</b>	<b>Economic model</b>	<b>Budget impact model</b>
Cost per script	-	\$  (effective price)	\$  (effective price)
Adherence	93-96% at 40 weeks <sup>a</sup>	100%	NA (market share approach)
Persistence	87-92% at 40 weeks	100%	NA (market share approach)
Cost/patient/year	-	\$  (effective price)	NA (market share approach)

Source: Table 3.6-1, p290; Table 4.1-1, pp310-311 of the submission; Section 4.6.3, p 100 of the SURPASS-2 trial report

Abbreviations: NA, not applicable

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

**Estimated PBS usage & financial implications**

6.88 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial implications of listing tirzepatide on the PBS/RPBS for the treatment of type 2 diabetes.

6.89 Key inputs for the financial estimates are summarised in Table 16.

**Table 16: Key inputs in the utilisation and financial estimates**

<b>Data</b>	<b>Value applied and source</b>	<b>Comment</b>
<b>Treatment utilisation</b>		
Projected semaglutide 0.5 mg scripts	Based on reported PBS scripts for semaglutide 0.5 mg (12080T), semaglutide 1 mg (12075M), dulaglutide 1.5 mg (11364D) dispensed in 2021.  Growth rates were based on scripts for the combined GLP-1 RA market (exenatide twice daily, exenatide once weekly, semaglutide 0.5 mg, semaglutide 1.0 mg and dulaglutide 1.5 mg) between June 2018 and August 2022 (prior to GLP-1 RA supply issues). These growth rates were extrapolated from 2022-2028 using exponential triple smoothing and then disaggregated by market share.	Extrapolation of historical growth trends based on the current PBS listings for GLP-1 RA therapies was unlikely to reflect utilisation under the draft PBS listings from the March 2023 PBAC review of T2DM restrictions. The revised listings are intended to limit use of GLP-1 RA therapies to patients failing SGLT2 inhibitor therapies (due to inadequate response, intolerance or contraindication) and by limiting the initiation of therapy to telephone/online authorities.  Additionally, the availability of GLP-1 RA therapies for type 2 diabetes was uncertain due to the recent supply shortages of semaglutide.
Projected semaglutide 1.0 mg scripts	Semaglutide 0.5 mg growth rates; -6.0% (2023), 11.8% (2024); 10.4% (2025); 9.7% (2026); 8.8% (2027); 8.2% (2028). Projected scripts increase from █ <sup>1</sup> in Year 1 to █ <sup>2</sup> scripts in Year 6.	

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Data	Value applied and source	Comment
Projected dulaglutide 1.5 mg scripts	Semaglutide 1 mg growth rates; 59.6% (2023), 24.5% (2024); 18.5% (2025); 15.4% (2026); 13.0% (2027); 11.5% (2028). Projected scripts increase from [redacted] <sup>3</sup> in Year 1 to [redacted] <sup>4</sup> in Year 6.  Dulaglutide 1.5 mg growth rates; 56.9% (2023), 11.1% (2024); 9.9% (2025); 9.1% (2026); 8.7% (2027); 8.0% (2028). Projected scripts increase from [redacted] <sup>4</sup> in Year 1 to [redacted] <sup>4</sup> scripts in Year 6.	
Estimated use without insulin	Semaglutide: 89.1%, dulaglutide: 85%  Based on a sponsor-commissioned analysis of a 10% sample of PBS data. The analysis assessed the coadministration (defined as scripts dispensed within 3 months of each other) of insulin and either semaglutide or dulaglutide between January 2022 and August 2022. The number of patients with co-administered insulin was then compared to the number of patients receiving GLP-1 RA in other combinations (GLP-1 RA + metformin; GLP-1RA + metformin + sulfonylurea).  The submission assumed that combination use remained constant over time.	The submission did not adequately justify the time period of the analysis (< 1 year).  The definition for co-administration used in the 10% PBS sample did not adequately account for the variable dosing of insulin (based on the dosing used in the model each insulin script would cover 6 months of therapy).  The estimated number of patients using other combinations did not appear to account for GLP-1 RA monotherapy (use outside the restriction) and GLP-1 RA + sulfonylurea.  The submission did not justify the assumption that combination use would remain constant over time.
Uptake rate	[redacted] <sup>1</sup> % in Year 1 increasing to [redacted] <sup>2</sup> % in Year 6. Assumption based on uptake of dulaglutide compared to other GLP-1 RA therapies before the availability of semaglutide with higher uptake expected due to superior glycaemic control and weight reduction.	Estimated uptake rates are highly uncertain given the rapidly changing dynamics of the GLP-1 RA market (as seen by the introduction of semaglutide).  Market research presented with the submission (Attachment 6) indicated that: - [redacted] <sup>3</sup> % (based on GPs) to [redacted] <sup>4</sup> % (based on specialists) of injection-naïve patients would be treated with tirzepatide versus GLP-1 RA therapies - [redacted] <sup>3</sup> % (based on GPs) to [redacted] <sup>4</sup> % (based on specialists) of patients would switch from an existing GLP-1 RA to tirzepatide

Source: Table 4.1-1 pp310-311 of the submission

Abbreviations: DPMQ, dispensed price per maximum quantity; GLP-1 RA glucagon-like peptide-1 receptor agonists; PBS, Pharmaceutical Benefits Scheme; SGLT2, sodium-glucose co-transporter 2 inhibitors

The redacted values correspond to the following ranges:

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

<sup>2</sup>600,000 to < 700,000

<sup>3</sup>900,000 to < 1,000,000

<sup>4</sup>1,000,000 to < 2,000,000

6.90 The estimated utilisation and financial implications (using effective prices) of a PBS/RPBS listing of tirzepatide for type 2 diabetes is summarised in Table 17.

**Table 17: Estimated utilisation and financial impact of listing tirzepatide on the PBS/RPBS (effective price)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total GLP-1 RA scripts without insulin	█ <sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>10</sup>	<sup>10</sup>	<sup>10</sup>
Uptake rate	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %
Total tirzepatide scripts	█ <sup>2</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost to PBS/RPBS less co-payment (\$)	█ <sup>3</sup>	<sup>7</sup>	<sup>8</sup>	<sup>8</sup>	<sup>11</sup>	<sup>11</sup>
Cost offset less co-payment for substituted semaglutide (\$)	█ <sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>
Cost offset less co-payment for substituted dulaglutide (\$)	█ <sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>
<b>Net PBS/RPBS cost (\$)</b>	█ <sup>5</sup>	█ <sup>3</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>7</sup>	█ <sup>7</sup>

Source: Table 4.2-2 p312; Table 4.2-3 p 314; p 4.2-4 314; Table 4.2-7 p317; Table 4.2-8 p317; Table 4.3-1 p319; Table 4.3-2 p320; Table 4.4-1 p321 of the submission

Abbreviations: DPMQ, dispensed price per maximum quantity; GLP-1 RA glucagon-like peptide-1 receptor agonists; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

- <sup>1</sup> 2,000,000 to < 3,000,000
- <sup>2</sup> 700,000 to < 800,000
- <sup>3</sup> \$100 million to < \$200 million
- <sup>4</sup> net cost saving
- <sup>5</sup> \$90 million to < \$100 million
- <sup>6</sup> 1,000,000 to < 2,000,000
- <sup>7</sup> \$300 million to < \$400 million
- <sup>8</sup> \$400 million to < \$500 million
- <sup>9</sup> \$200 million to < \$300 million
- <sup>10</sup> 3,000,000 to < 4,000,000
- <sup>11</sup> \$500 million to < \$600 million

- 6.91 The net cost to the PBS/RPBS was \$90 million to < \$100 million in Year 1, increasing to \$300 million to < \$400 million in Year 6, with a cumulative net cost of > \$1 billion over the first 6 years of listing.
- 6.92 The estimates presented in the submission were largely uninformative as they were based on historical growth trends for GLP-1 RA therapies which were unlikely to reflect the utilisation of GLP-1 RA therapies in the future. The PBAC recently recommended revisions to the GLP-1 RA restrictions which are intended to narrow eligibility to patients who have previously failed SGLT2 inhibitor therapies (due to inadequate response, intolerance or contraindication) while also requiring a higher authority level for treatment initiation in order to reduce use outside of restrictions (para 5.15, PBS restrictions for type 2 diabetes mellitus medicines, March 2023 PBAC meeting). The PSCR stated that it is difficult to predict the likely future use of GLP-1 RA therapies resulting from the proposed changes in restriction and product shortages. The ESC agreed with the evaluation that the historical growth rates are unlikely to reflect the utilisation of these medicines in the future. The ESC also noted product shortages are of ongoing concern and considered tirzepatide was likely to be met with the same or

even greater enthusiasm for weight loss as semaglutide<sup>4</sup>. The pre-PBAC response maintained that, in the absence of alternative sources and in line with current clinical practice, the use of historical data to estimate predicted utilisation remained the best source of evidence.

- 6.93 The ESC noted the brief sensitivity analyses presented in the submission. The ESC considered that given the level of uncertainty and the magnitude of the estimated cost, it would be informative to have more ranges considered for key parameters in the sensitivity analyses, which considered projected GLP-1 RA market size, the expected proportion of GLP-1 RA use with insulin and tirzepatide uptake rates.

### **Quality Use of Medicines**

- 6.94 The submission stated that the sponsor will undertake pharmacovigilance activities to manage any risks associated with tirzepatide treatment.
- 6.95 Expert advice provided with the submission raised concerns regarding the need for pharmacies to stock the six different tirzepatide dose strengths as well as concerns about the reliable supply of each dose strength in order to allow for adequate dose titration. During the evaluation, it was noted that tirzepatide has been subject to drug shortages in the United States due to increased demand (FDA drug shortage list, 22 March 2023).
- 6.96 Additionally, the submission has not addressed the use of tirzepatide 2.5 mg, 7.5 mg and 12.5 mg as maintenance doses despite requesting sufficient repeats to cover 6 months of therapy with these dose strengths.

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

- 6.97 The submission did not propose a risk-sharing arrangement.  
*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 as dual therapy in combination with metformin. 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, but 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 considered that the incremental cost-

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<sup>4</sup> Jastreboff, A. M., et al. (2022). " Tirzepatide Once Weekly for the Treatment of Obesity." *N Engl J Med* 387(3):205-216.

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.

- 7.2 The PBAC considered the primary reason for this outcome was due to the economic evaluation provided.
- 7.3 The PBAC noted the comments from individuals, health care professionals and organisations which highlighted benefits of treatment with tirzepatide including significant reduction in glycated haemoglobin (HbA1c) and weight loss. The comments also highlighted the importance of having multiple therapeutic options for Australians living with difficult to manage type 2 diabetes to address supply shortages. The PBAC specifically noted and was sympathetic to the notion proposed by the National Aboriginal Community Controlled Health Organisation (NACCHO) that glucagon-like peptide-1 (GLP-1) analogues and tirzepatide be included on the PBS list for Aboriginal and Torres Strait Islander peoples under a Streamline Authority for those with type 2 diabetes or pre-diabetes with obesity with no further restrictions (see paragraph 6.6). The PBAC would welcome a proposal to address the needs of this higher risk group of patients in a future resubmission.
- 7.4 The PBAC considered that the nomination of semaglutide as the main comparator and dulaglutide as a secondary comparator was appropriate.
- 7.5 With respect to the restriction, the PBAC considered the requested alignment of the restriction with the March 2023 PBAC review of the T2DM restrictions was appropriate. The PBAC noted the number of repeats for titration doses are not limited for semaglutide, however, given multiple titration phases for tirzepatide the PBAC agreed with the ESC 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 (see paragraph 3.3). In addition, the PBAC agreed with the ESC that it was likely that clinicians would want to also use tirzepatide in combination with sulfonylurea or insulin given available clinical data within the type 2 diabetes trial program (SURPASS-4, SURPASS-5, SURPASS-AP-COMBO) and thus there was a high risk of use in clinical practice beyond the proposed restriction. It was noted that no Risk Sharing Arrangement (RSA) had been proposed in the submission.
- 7.6 The PBAC noted the key clinical trials, SURPASS-2 (tirzepatide vs semaglutide) and SUSTAIN 7 (semaglutide vs dulaglutide), were open-label randomised active-control trials and that there was differential discontinuation between arms in the SURPASS-2 trial. The PBAC agreed with the evaluation and ESC that the risk of bias in the key trials was high.
- 7.7 The PBAC noted the submission described tirzepatide 5 mg once weekly as superior in terms of efficacy compared to semaglutide 0.5 mg once weekly and tirzepatide 10 mg or 15 mg once weekly as superior to semaglutide 1 mg once weekly based on HbA1c

and weight loss benefits. While the submission did not make a clinical claim for tirzepatide 5 mg once weekly versus semaglutide 1 mg once weekly, the PBAC agreed with the ESC that this comparison remained relevant given that submission requested a higher price for low dose tirzepatide compared to high dose semaglutide (see paragraph 6.49).

- 7.8 The PBAC noted the results of the SURPASS-2 trial indicated treatment with tirzepatide 5 mg, 10 mg or 15 mg was associated with statistically significant reductions in HbA1c from baseline to Week 40 compared with semaglutide 1 mg. The PBAC noted that, while statistically significant reductions were evident using both treatment regimen estimand and efficacy estimand analyses, the nominated minimal clinically important difference (MCID) was only exceeded for tirzepatide 10 mg or 15 mg compared to semaglutide 1 mg using the efficacy estimand. The PBAC noted ESC advice that the efficacy estimand analyses presented in the submission may be considered a legitimate approach (see paragraph 6.20). The PBAC also noted the treatment with tirzepatide 10 mg and 15 mg weekly was associated with a statistically significant increase in the proportion of patients achieving <7.0% and <5.7% HbA1c targets compared to semaglutide 1 mg weekly.
- 7.9 The PBAC considered the results of the SURPASS-2 trial indicated treatment with tirzepatide 5 mg, 10 mg and 15 mg was associated with statistically significant short-term reductions in body weight at Week 40 (treatment regimen estimand), with treatment differences of -1.9 kg (95% CI -2.8, -1.0), -3.6 kg (95% CI -4.5, -2.7) and -5.5 kg (95% CI -6.4, -4.6) respectively compared to semaglutide 1 mg. The PBAC noted that treatment differences for tirzepatide 10 mg and 15 mg versus semaglutide 1 mg were clinically important, with point estimates exceeding the nominated MCID of 3 kg.
- 7.10 Noting that the clinical claim of superiority was based on HbA1c and weight loss benefits the PBAC highlighted that the long-term comparative efficacy of tirzepatide is unknown, with only short-term data presented from the key trial (40 weeks). The PBAC reaffirmed previous advice that the clinical relevance of change in HbA1c may shift in the context of changing treatment algorithms based on patient-centred outcomes (para 7.5, semaglutide PSD, November 2019 PBAC meeting). The PBAC also reaffirmed previous concerns regarding the lack of long-term data supporting reductions in downstream complications for treatments claiming weight loss benefits (semaglutide for obesity PSD, March 2022 PBAC meeting; semaglutide for type 2 diabetes PSD, November 2019 PBAC meeting). However, based on HbA1c and short-term weight loss benefits the PBAC considered that tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly was superior in terms of effectiveness compared to semaglutide 1 mg once weekly, but this claim was not supported for tirzepatide 5 mg once weekly compared to semaglutide 1 mg once weekly. The PBAC considered that the claim of superior comparative effectiveness was reasonable for tirzepatide 5 mg once weekly compared to semaglutide 0.5 mg once weekly.
- 7.11 The PBAC noted the higher incidence of serious adverse events and adverse events leading to discontinuation for tirzepatide 5 mg, 10 mg and 15 mg once weekly

compared to semaglutide 1 mg once weekly. The PBAC also noted the higher incidence of treatment-related adverse events and gastrointestinal events for tirzepatide 10 mg and 15 mg once weekly compared to semaglutide 1 mg once weekly. The PBAC noted the inflexible dosing in the trial setting contributed to side-effects experienced at the higher doses but also considered these side effects may limit titration to higher doses in clinical practice. Overall, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data for any of the comparisons.

- 7.12 The PBAC noted the submission 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 use of a flat pricing structure (see paragraph 6.58).
- 7.13 The modelled circumstances of use were based on assumptions of 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. The PBAC noted that 8.3% to 13.2% of patients in the SURPASS-2 trial discontinued therapy (see Table 12). In addition, the PBAC agreed with the ESC 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. As such, the PBAC considered the submissions assumptions regarding modelled circumstances of use are unlikely to reflect Australian clinical practice.
- 7.14 The submission estimated the drift in HbA1c values over time based on the United Kingdom Prospective Diabetes Study Outcome Model 2 risk equation and assumed no drift for other biomarkers (see Table 12). The PBAC considered the assumption of no drift in other biomarkers in the economic model was not clinically appropriate and, based on the results presented in the sensitivity analysis (see Table 14), favoured tirzepatide.
- 7.15 The PBAC noted the concerns raised by the ESC regarding the approach taken by the submission to applying weight-based utility/disutility values (see paragraph 6.72) and considered the modelled approach unreliable. The PBAC also noted the concerns raised by the ESC regarding the application of a flat rate disutility value of 0.005 per non-severe daytime hypoglycaemic episode (see paragraph 6.73). The PBAC agreed with the ESC that the flat rate disutility value lacked face validity and that the submission also substantially overestimated hypoglycaemia rates with insulin compared to GLP-1 RA/GIP therapies (1,400 versus 0.47-2.12 per 100 patient years). The PBAC noted the ESC advised that the high rate of hypoglycaemia events when combined with the application of a high flat rate disutility value per event was an important driver of the model.
- 7.16 The PBAC noted that treatment with tirzepatide was associated with an incremental cost per QALY gained of \$115,000 to <\$135,000 for the 5 mg dose,

\$55,000 to < \$75,000 for the 10 mg dose and \$45,000 to < \$55,000 for the 15 mg dose compared to semaglutide 1 mg weekly. The PBAC agreed with the ESC that the ICERs per QALY gained were high, particularly for those based on lower doses, and all ICERs were likely under-estimated due to optimistic assumptions, particularly around utility weights and insulin intensification. The PBAC agreed with the ESC that optimistic assumptions around utility weights, biomarker drift and insulin intensification should be addressed in a revised base case that incorporated:

- Constant eGFR treatment effects
- UKPDS drift for all biomarkers
- Insulin intensification at HbA1c 8.0%
- Reduced hypoglycaemia disutility to -0.003 per event.

The PBAC noted that even without addressing all the issues regarding circumstances of use (paragraph 7.13) or weight-based utility/disutility (paragraph 7.15) the scenario analyses based on the 4 points above increased the base case ICER from \$115,000 to < \$135,000 to \$255,000 to < \$355,000 per QALY gained for the 5 mg dose, from \$55,000 to < \$75,000 to \$115,000 to < \$135,000 per QALY gained for the 10 mg dose and from \$45,000 to < \$55,000 to \$75,000 to < \$95,000 per QALY gained for the 15 mg dose. The PBAC considered that the resulting ICERs were high and advised that an ICER in the order of \$30,000 per QALY would be appropriate. As such, the PBAC noted a substantial price reduction would be required for the proposed listing to be considered cost-effective.

7.17 The PBAC noted concerns raised by the evaluation and the ESC regarding the use of historical growth trends of GLP-1 analogues to estimate the PBS usage and financial implications of a tirzepatide listing given recent recommendations to narrow eligibility of such therapies (see paragraph 6.92). The PBAC agreed with the ESC that additional sensitivity analyses in this area may assist in understanding some of the uncertainty regarding future growth in GLP-1 RA use (see paragraph 6.93). The PBAC considered that the financial impact was uncertain and extremely high at the requested price.

7.18 The PBAC considered a resubmission for tirzepatide should address the following issues:

- Provide an economic model which addresses the issues regarding circumstances of use (see paragraph 7.13) and weight-based utility/disutility (see paragraph 7.15), includes revisions outlined in paragraph 7.16 and a substantial 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 7.17.

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

7.19 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.