An addendum to this public summary document has been included at the end of the document.

5.17 TEPROTUMUMAB, Powder for I.V. infusion 500 mg, Tepezza®, AMGEN AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required (STREAMLINED), listing for teprotumumab for the treatment of active, moderate-to-severe (MS) thyroid eye disease (TED).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC) consisting of IV methylprednisolone (IVMP) with or without mycophenolate mofetil (MMF) in the first-line (1L) setting and tocilizumab in the second-line (2L) setting.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Active, moderate-to-severe thyroid eye disease (TED)
Intervention	Teprotumumab (Tepezza); an IGF-1R inhibitor administered as an IV infusion once every 3 weeks for a total of 8 doses.
Comparator	Standard of care: 1st line: IV methylprednisolone (IVMP) with or without MMF 2nd line: tocilizumab
Outcomes	• Proptosis • Diplopia • Overall response[a] • Health-related Quality of Life (GO-QoL) • Adverse Events
Clinical claim	Teprotumumab is superior in terms of efficacy and non-inferior (with the strong possibility of superiority) in terms of safety compared to IVMP (+/-MMF) [1st line]. Teprotumumab is superior in terms of efficacy and non-inferior in terms of safety compared to tocilizumab [2nd line] for the treatment of active, moderate-to-severe TED, based on the available evidence. The Pre-Sub-Committee response (pp3−4) further clarified that the safety profiles of teprotumumab are 'non-inferior but different'.

Source: Table 1-1, p2 of the submission.
IGF-1R = insulin-like growth factor-1 receptor; IVMP = intravenous methylprednisolone; GO-QoL = Graves' ophthalmopathy quality of life; MMF = mycophenolate mofetil; TED = thyroid eye disease; SOC = standard of care
Note: IVMP is commonly dosed at 500 mg weekly for 6 weeks, then 250 mg weekly for 6 weeks and MMF is dosed at 720 mg/day for 6 weeks.
[a]Overall response was defined as ≥2 mm reduction in proptosis AND a ≥2 point reduction in Clinical Activity Score (CAS) from Baseline in the study eye, without deterioration (≥2 mm increase in proptosis or ≥2 point increase in CAS) in the fellow eye at Week 24.

2 Background

Registration status

2.1 At the time of PBAC consideration, teprotumumab was undergoing priority review by the TGA for the 'treatment of Thyroid Eye Disease (TED)'. The TGA Delegate's Overview was available. While a decision was yet to be made, the Delegate was inclined to consider the registration of teprotumumab, if appropriate measures were in place to create a favourable benefit-risk balance, pending Advisory Committee on Medicines (ACM) advice. Were the registration supported, the Delegate would likely propose additional conditions of registration.

2.2 In December 2024, the ACM provided advice to the TGA Delegate. The ACM considered that patients should be screened for hearing impairment prior to treatment, due to a noted higher level of hearing impairment for patients with pre-existing hearing loss. The ACM also suggested ongoing monitoring with serial audiograms in addition to a boxed warning explaining the risk of possible permanent hearing impairment.

2.3 The ACM also considered that it would be appropriate to limit the TGA indication to MS TED. Additionally, the ACM supported limiting the indication to an adult population due to the mechanism of action and effects on growth and development, and inclusion of a boxed warning for the risk of major foetal malformation.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
teprotumumab					
Initial					
Teprotumumab 500 mg, injection, 1 vial.	Public $[redacted] published price $[redacted] effective price Private $[redacted] published price $[redacted] effective price	3	3	0	Tepezza
Continuing					
Teprotumumab 500 mg, injection, 1 vial	Public $[redacted] published price $[redacted] effective price Private $[redacted] published price $[redacted] effective price	6	6	6	Tepezza

Category / Program: Section 100
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Administrative Advice: No increase in the maximum number of repeats may be authorised. Increased maximum quantity will be authorised where a patient's weight is greater than 150 kg. Authority applications for increased quantities/ repeats (where relevant) may be made by telephone to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Severity: moderate to severe
Condition: Thyroid eye disease
Indication: Active, moderate-to-severe thyroid eye disease
Treatment Phase: Initial
Clinical criteria:
Patient must have a clinical activity score (CAS) of three or more for the most severely affected eye,
AND
Clinical criteria:
Patient must have two or more of the following: - Proptosis ≥3 or mm above normal for race and gender - Lid retraction ≥2mm - Moderate–to–severe soft-tissue involvement - Inconstant or constant diplopia
Treatment criteria:
Must be treated by a specialist physician experienced in the treatment of thyroid eye disease

Category / Program: Section 100
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Administrative Advice: No increase in the maximum number of repeats may be authorised. Increased maximum quantity will be authorised where a patient's weight is greater than 150 kg. Authority applications for increased quantities/ repeats (where relevant) may be made by telephone to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Severity: moderate to severe
Condition: Thyroid eye disease
Indication: Active, moderate-to-severe thyroid eye disease
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
Treatment criteria:
Must be treated by a specialist physician experienced in the treatment of thyroid eye disease

3.1 The submission proposed a special pricing arrangement (SPA), with a published ex-manufacturer price (EMP) of $[redacted] and an effective EMP of $[redacted] per vial.

3.2 The proposed PBS restriction is narrower than the proposed TGA indication. The proposed TGA indication for teprotumumab is for the treatment of TED, whereas the

proposed PBS listing restricts treatment to moderate-to-severe TED. The proposed PBS listing also requires a minimum clinical activity score (CAS).

3.3 The proposed CAS of ≥ 3 for the most severely affected eye was lower than the inclusion criteria for the key teprotumumab trials where patients must have had a CAS of ≥ 4. The submission justified this by noting that the definition of active TED is a CAS of ≥ 3. The ESC considered that the proposed CAS threshold was likely reasonable, noting that optimal treatment outcomes were contingent on administration within a critical therapeutic window and that the classification of the severity of TED (as reported in the 2021 European Group on Graves' Orbitopathy [EUGOGO] guidelines) was included as a separate clinical criterion and would likely ensure that only patients with moderate-to-severe TED access treatment.

3.4 The proposed listing does not include a requirement for a diagnosis of a thyroid related disorder. The inclusion criteria for the key teprotumumab trials required that patients have a diagnosis of Graves' disease (GD), the most common cause of TED. The submission noted that restricting teprotumumab to patients with GD would exclude approximately 10% of patients with TED. Data for these patients were not included in the submission, however the DUSC considered that it was appropriate to not limit treatment to patients with GD.

3.5 The ESC noted that the submission requested a line agnostic listing for teprotumumab. However, the key teprotumumab trials only enrolled patients in the 1L setting. The submission provided two references to studies in support of teprotumumab use in steroid-resistant MS TED patients: a case control study (N=31) (Toro Tobon et al. 2023)[1] and a retrospective study (N=76) (Men et al. 2024)[2]. Both studies report a clinical response after teprotumumab use in treatment experienced patients (discussed further in paragraph 6.56). The Pre-Sub-Committee Response (PSCR) maintained that a line agnostic listing was appropriate and was supported by local clinical experts and the previously noted studies. The ESC considered that based on the available evidence, it was uncertain whether a line agnostic listing was appropriate, particularly without further criteria in the setting of retreatment (see paragraph 3.6 below).

3.6 The ESC noted that the proposed listing does not place any restrictions on when or under what circumstances retreatment may occur. The draft Product Information and the requested listing allow for an infusion every 3 weeks for a total of 8 infusions. No information is given for time between courses if retreatment were to be initiated. In the extension trial, OPTIC-X, retreatment was given to proptosis non-responders from the OPTIC trial who completed the month 12 visit and proptosis responders who

[1] Toro-Tobon D, Rachmasari KN, Bradley EA, Wagner LH, Tooley AA, Stokken JK, Stan MN. Medical Therapy in Patients with Moderate to Severe, Steroid-Resistant, Thyroid Eye Disease. *Thyroid*. 2023 Oct;33(10):1237-44.

[2] Men, C. J., Amarikwa, L., Sears, C., Shinder, R., Clauss, K., Ugradar, S., Cockerham, K., Wester, S., Douglas, R., & Kossler, A. (2024) Teprotumumab for the Treatment of Recalcitrant Thyroid Eye Disease. *Ophthalmic Plast Reconstr Surg* 40(4), 276-285.

relapsed during the follow-up period of the OPTIC trial and completed the Week 24 visit. The ESC noted that ophthalmologists would likely retreat patients as required to avoid surgery and considered that retreatment may be appropriate for subsequent episodes of active MS TED, but not for episodes that occur due to lack of response to 1L treatment. The pre-PBAC Response noted that the proposed restriction limits access to patients who meet both the disease severity and activity requirements. Therefore, the restriction preludes access to patients with chronic (inactive) TED (defined by CAS<3). The Response considered that the majority of patients that require retreatment are identified early in the disease course while in the active phase. In these situations, clinicians have stated they would likely switch treatment rather than retreat with the same agent. However, there may be situations where retreatment is clinically warranted, and the Response noted that the sponsor would be supportive of the inclusion of a retreatment criterion.

3.7 The requested listing did not include any stopping or continuation criteria. The key teprotumumab trials had stopping criteria based on adverse events (AEs), lack of efficacy, non-compliance, loss to follow-up, and pregnancy. The DUSC considered that while it was appropriate for the continuing treatment phase to not include a response criterion, a stopping rule should be considered. The DUSC also considered that continuing scripts should be prescribed by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease to improve access and logistics for patients, particularly in rural and remote patients.

3.8 The submission requested a Section 100 listing, with Authority Required (Written) for the initial restriction and Authority Required (streamlined) for the continuing restriction. The DUSC considered that an Authority Required (telephone/online) immediate assessment (no human operator) was more suitable for the initial restriction.

3.9 The DUSC considered that treatment should be restricted to adults 18 years of age or older due to the mechanism of action and effects on growth and development.

3.10 The DUSC considered that due to the unknown mechanism of action of the hearing loss associated with teprotumumab and higher rates in real world studies, it would be appropriate to include a requirement in the restriction for audiology review and surveillance prior to and during treatment with teprotumumab. The pre-PBAC acknowledged that hearing impairment was an important risk associated with teprotumumab and agreed with the proposed amendment to the restriction.

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

4 Population and disease

4.1 TED is an autoimmune inflammatory disorder that primarily affects the orbit and periorbital tissues[3]. It is most commonly associated with GD but can also occur in other thyroid conditions, such as Hashimoto's thyroiditis[4]. TED significantly impacts patients' quality of life (QoL) due to its ocular manifestations, which can range from mild discomfort to vision-threatening complications[5].

4.2 Clinically, TED presents with a wide spectrum of signs and symptoms. The most common is eyelid retraction. Proptosis, or forward protrusion of the eyeball, periorbital oedema and conjunctival redness are frequently observed due to inflammation of the orbital tissues. Patients often report double vision (diplopia), which arises from the involvement of the extraocular muscles. Severe cases may lead to optic neuropathy, where compression of the optic nerve results in progressive vision loss. Exposure keratopathy, caused by incomplete eyelid closure, can further exacerbate ocular morbidity[2].

4.3 Assessment of TED involves evaluating disease activity and severity. The CAS (Table 2) is commonly used to distinguish between the active (inflammatory) and inactive (fibrotic) phases of the disease. CAS evaluates signs of inflammation, such as pain, redness, and swelling[6]. Each positive symptom contributes 1 point with a CAS of ≥ 3 indicating active TED.

Table 2: Assessment of thyroid eye disease by the clinical activity score (CAS)

	Assessment of activity
1.	Spontaneous retrobulbar pain
2.	Pain on attempted upward or downward gaze
3.	Redness of eyelids
4.	Redness of conjunctiva
5.	Swelling of caruncle or plica
6.	Swelling of eyelids
7.	Swelling of conjunctiva (chemosis)

Source: Table 1-2, p8 of the submission

4.4 The EUGOGO has established a severity scale to classify TED into mild, moderate-to-severe, and sight-threatening categories (Table 3). This classification is based on clinical features such as proptosis, diplopia, and corneal exposure[7].

[3] Weiler DL. Thyroid eye disease: a review. *Clin Exp Optom*. 2017 Jan;100(1):20-5.
[4] Rashad R, Pinto R, Li E, Sohrab M, Distefano AG. Thyroid Eye Disease. *Life (Basel)*. 2022 Dec 12;12(12)
[5] Cockerham KP, Padnick-Silver L, Stuertz N, Francis-Sedlak M, Holt RJ. Quality of Life in Patients with Chronic Thyroid Eye Disease in the United States. *Ophthalmol Ther*. 2021 Dec;10(4):975-87
[6] Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. Eur Thyroid J. 2022 Dec 1;11(6)
[7] Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. European Journal of Endocrinology. 2021;185(4):G43-G67

Table 3: Classification of severity of TED (as reported in the 2021 EUGOGO guidelines)

Classification	Features
Mild	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos <3 mm above normal for race and gender • no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: • lid retraction ≥ 2 mm • moderate or severe soft-tissue involvement • exophthalmos ≥ 3 mm above normal for race and gender • inconstant or constant diplopia
Sight-threatening (very severe)	Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown

Source: Table 1-3, pp8-9 of the submission.
EUGOGO = European group on Graves' orbitopathy; GO = Graves' orbitopathy; TED = thyroid eye disease.

4.5 The two main outcomes measured in the key teprotumumab trials, proptosis (also called exophthalmos) and diplopia, are important features in the EUGOGO guidelines, with proptosis of ≥ 3mm above normal for a patient's race and inconstant or constant diplopia being indications of MS TED.

4.6 The natural history of TED typically follows a biphasic course. The active phase, lasting 1 to 3 years, is characterised by progressive inflammation and tissue remodelling[8]. Early intervention during this phase is crucial to prevent irreversible damage. The disease eventually stabilises, transitioning into the inactive phase, where inflammation subsides but residual fibrosis may result in persistent symptoms, such as restricted eye movements or cosmetic disfigurement[6].

4.7 The submission has requested a line agnostic listing for teprotumumab for the treatment of active MS TED[9]. Currently, active MS TED is treated using IVMP with or without MMF. Although the submission has placed tocilizumab in the 2L setting of the current clinical management algorithm, the evaluation considered that it was uncertain to what extent it was used in Australia as it does not currently have a PBS listing for use in TED with access relying on special or compassionate access schemes. The ESC considered that rituximab may also be used in the 2L setting.

4.8 Teprotumumab is a fully human monoclonal antibody that targets the insulin-like growth factor 1 receptor (IGF-1R), an important pathway in the pathogenesis of TED. By inhibiting IGF-1R, teprotumumab disrupts the interaction between IGF-1R and the thyroid-stimulating hormone receptor (TSHR), which drives the autoimmune and

[8] Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the Treatment of Active Thyroid Eye Disease. *N Engl J Med*. 2020 Jan 23;382(4):341-52
[9] Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Engl J Med*. 2017 May 4;376(18):1748-61.

inflammatory processes underlying TED. This mechanism helps reduce fibroblast activation, tissue inflammation, and orbital remodelling, directly addressing the underlying causes of the disease[10].

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

5 Comparator

5.1 The submission nominated SoC consisting of IVMP with or without MMF as the main comparator. The main reasons provided in support of this nomination were that IVMP with or without MMF is recommended by both local and international guidelines as the 1L treatment for active MS TED[11,12]. The ESC considered IVMP with or without MMF was an appropriate comparator for teprotumumab in the 1L setting.

5.2 The submission nominated tocilizumab as a comparator for the second-line treatment of TED. The submission based this on local opinion leader input and international recommendations. It is uncertain to what extent tocilizumab is used in Australia to treat TED. Tocilizumab does not currently have registration by the TGA or PBS for this indication. The Royal Victorian Ear and Eye Hospital guidelines note that access to tocilizumab is dependent upon special or compassionate access. The PSCR considered tocilizumab had the strongest supporting evidence in the 2L setting and maintained that it was the appropriate comparator. The PSCR acknowledged that patient access is challenging and involves named patient compassionate access in the public system as well as private (off-label) use. The ESC noted that the 2L treatment of MS TED was not well defined, however considered that rituximab may also be a relevant comparator in the 2L setting, noting that it has an unrestricted PBS listing.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The first clinician discussed the natural history of MS TED, highlighting that TED is characterised by progressive inflammation, eye protrusion, debilitating double vision and is vision threatening. The clinician noted the high and unmet clinical need for alternative therapies, outlining current Australian clinical practice and the typical outcomes for patients. The clinician emphasised that current first-line treatment options (intravenous corticosteroids) are non-specific and

[10] Smith TJ. TSHR-IGF-IR complex drives orbital fibroblast misbehavior in thyroid eye disease. *Curr Opin Endocrinol Diabetes Obes*. 2024 Oct 1;31(5):177-83

[11] The Royal Victorian Eye and Ear Hospital. CLINICAL PRACTICE GUIDELINE: Emergency Department Thyroid-Associated Orbitopathy. 2023

[12] Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. European Journal of Endocrinology. 2021;185(4):G43-G67

have minimal impact on the severity of disease, with a high proportion of patients experiencing disease progression and relapse within 6 months. The clinician considered that it was appropriate for the PBS restriction to be based on the OPTIC trial criteria and that expected use would predominately be as first-line treatment. The second clinician stated that treatment with teprotumumab led to predictable proptosis reduction, improved extraocular motility, reduced soft tissue inflammation, improved quality of life and considered the side effect profile to be manageable. The clinician outlined their experience and potential side effects from treatment with teprotumumab, noting the importance of a baseline audiogram for all patients prior to treatment, and continuous monitoring for hearing loss during and at the conclusion of treatment. The clinician noted that immediate infusion reactions were rare and that less than 5% of patients discontinued teprotumumab due to serious adverse events. The clinician stated that treatment with teprotumumab also reduced the amount and degree of surgery required for their patients. The clinician stated that clinical regression may occur for some patients treated with teprotumumab and some patients may experience a disease flare. The clinician noted that of approximately 200 patients they had treated with teprotumumab, 5−10 patients had required retreatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (11), health care professionals (14) and organisations (5) via the Consumer Comments facility on the PBS website.

6.3 The health care professionals (HCPs) noted there was an unmet clinical need for effective and disease specific therapies for patients with TED in Australia. The HCPs commented on the clinical benefits associated with teprotumumab over current SOC, noting that teprotumumab targeted the underlying pathophysiology of TED, and that based on the clinical trial evidence, teprotumumab was associated with significant improvements in CAS, proptosis, and diplopia versus SOC and would likely lead to a reduction in vision loss and the need for continuous steroid use and invasive surgeries. The HCPs also considered treatment with teprotumumab would be associated with a number of quality-of-life benefits and enable patients to better engage in their routine daily activities. The HCPs noted that teprotumumab was generally well-tolerated and considered that side effects could be managed through careful screening and monitoring.

6.4 The individuals who commented comprised of TED patients who would like access to teprotumumab (10) and 1 other interested individual. The comments from individuals emphasised the high burden of disease and suffering associated with TED. The comments described the symptoms experienced and how it impacted on their daily lives, including ocular motility issues and double vision prevention the ability to work effectively, particularly on screens, and lid retraction, proptosis and dry eye

preventing individuals from keeping their eyes open for extended periods without pain and watering. Individuals emphasised that the symptoms experienced severely impacted on their ability to work, exercise, socialise, and partake in their usual activities and hobbies, which severely affected their psychological wellbeing. Individuals also noted they required assistance with essential everyday activities, such as reading, driving, shopping, and cooking. Individuals also noted the challenges posed by what was described as a fragmented treatment landscape in Australia, noting that consultations with multiple medical professionals had led to a difference in opinion and suboptimal outcomes. Individuals also noted that the cost of teprotumumab was currently a significant barrier to treatment and considered that the listing of teprotumumab on the PBS would ensure equitable access to treatment.

6.5 The PBAC noted advice received from the Australian and New Zealand Strabismus Society (ANZSS), the Australia and New Zealand Society of Ophthalmic Plastic Surgeons (ANZSOPS), the International Thyroid Eye Disease Society, the Global Healthy Living Foundation Australia, and the Australian Thyroid Foundation, supporting the PBS listing of teprotumumab for the treatment of active MS TED.

6.6 The input from organisations noted that there is currently an unmet clinical need for effective and disease specific therapies for patients with active TED in Australia. Current SoC primarily focuses on the management of symptoms associated with TED; however, these therapies often yield limited clinical response, with minimal improvement in proptosis and diplopia. The input emphasised that TED is a debilitating disorder, which can lead to facial disfigurement and impaired vision, which often leads to a loss of social confidence, an inability to participate in daily activities and can ultimately lead to social isolation. These effects can lead to a significantly reduced quality of life and have a severe impact on the mental health of affected individuals. Input from organisations noted that based on the clinical trial evidence, treatment with teprotumumab was associated with a significant reduction in proptosis and diplopia and improvement in CAS and quality of life metrics compared to placebo, with patients reporting less eye pain, reduced double vision, and improved visual functioning. Organisations emphasised that teprotumumab would be a valued addition to treatment options for TED in Australia and would likely represent a major step forward in delivering effective and disease-modifying care.

Clinical studies

6.7 The submission was based on two head-to-head trials comparing teprotumumab to placebo, in addition to background medication for TED. TEDRV01 (n=88) enrolled patients with Graves' disease associated with active TED. OPTIC (n=83) enrolled patients with Graves' disease associated with active MS TED. Additionally, the OPTIC-X trial (n=51) enrolled patients who completed the 24-week double-masked treatment period of the OPTIC trial who were either proptosis non-responders at week 24 or had relapsed during the OPTIC follow-up period. This trial was provided as supporting evidence for retreatment with teprotumumab.

6.8 An unanchored matching adjusted indirect comparison (MAIC) was referenced to inform the comparison of teprotumumab to IVMP in the 1L setting[14]. This MAIC pooled patient data from TEDRV01 and OPTIC and compared it to aggregate data from IVMP studies, adjusting for baseline differences in age, sex, and smoking status. The analysis focused on changes in proptosis and diplopia at 24 weeks for teprotumumab and 12 weeks for IVMP.

6.9 A Bucher indirect treatment comparison (ITC) was conducted to inform the comparison of teprotumumab to tocilizumab in the 2L setting. The submission used pooled data from the TEDRV01 and OPTIC studies and compared it to the results reported by Perez-Moreiras et al., 2018[13] (n=32) using placebo as a common comparator.

6.10 Details of the teprotumumab studies presented in the submission are provided in

6.11 Table 4.

Table 4: Key trials included in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
Teprotumumab vs. placebo		
TEDRV01	Clinical study report: Phase 2 trial; TED01RV trial A multicenter, double-masked, placebo-controlled, efficacy and Safety study of teprotumumab (HZN-001), an insulin-like growth factor-1 receptor (IGF-1R) antagonist antibody (fully human), administered every 3 weeks (Q3W) by intravenous (IV) infusion in patients suffering from active thyroid eye disease (TED)	21 December 2018
	Smith, T.J., Kahaly, G.J., Ezra, D.G., Fleming, J.C., Dailey, R.A., Tang, R.A., Harris, G.J., Antonelli, A., Salvi, M., Goldberg, R.A. and Gigantelli, J.W. Teprotumumab for thyroid-associated ophthalmopathy.	New England Journal of Medicine 2017; 376(18): pp.1748-1761
	Douglas, R.S. Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active thyroid eye disease: a focus on proptosis.	Eye 2019; 33(2): pp.183-190.
	Conference abstract: Kahaly, GJ, Douglas, R, Holt, RJ, Perdok, R, Ball, J, Smith, TJ. 48-week follow-up of a multicenter, randomized, double-masked, placebo-controlled treatment trial of teprotumumab in thyroid-associated ophthalmopathy.	88th Annual Meeting of the American Thyroid Association. Thyroid® 2019; 28: P-1-A-158.
	Kahaly G, Douglas R, Holt R, et al. SAT-554 Teprotumumab in Graves' Orbitopathy: Extended Outcome Analyses.	Journal of the Endocrine Society 2019; **3**
OPTIC	Clinical study report: OPTIC trial A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Active Thyroid Eye Disease	24 April 2019

[13] Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, et al. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. *Am J Ophthalmol*. 2018 Nov;195:181-90.

Trial ID	Protocol title/ Publication title	Publication citation
	Clinical Study Report Addendum (Follow-Up Period) A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Active Thyroid Eye Disease	03 August 2020
	Clinical Study Report Addendum (Follow-Up Period) A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Active Thyroid Eye Disease	18 May 2021
	Douglas, R.S., Kahaly, G.J., Patel, A., Sile, S., Thompson, E.H., Perdok, R., Fleming, J.C., Fowler, B.T., Marcocci, C., Marinò, M. and Antonelli, A. Teprotumumab for the treatment of active thyroid eye disease.	New England Journal of Medicine 2020; 382(4): pp.341-352
Teprotumumab extension study		
OPTIC-X	Clinical study report: OPTIC-X trial Multicenter, Safety and Efficacy, Open-label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease	28 June 2021
	Clinical Study Report Addendum (follow-up period) Multicenter, Safety and Efficacy, Open-label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)	28 June 2021
	Douglas, R.S., Kahaly, G.J., Ugradar, S., Elflein, H., Ponto, K.A., Fowler, B.T., Dailey, R., Harris, G.J., Schiffman, J., Tang, R. and Wester, S., 2022. Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment: OPTIC-X study.	Ophthalmology 2022; 129(4): pp.438-449.
Teprotumumab vs. IVMP MAIC		
Douglas et al., 2022	Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, et al. Proptosis and Diplopia Response With Teprotumumab and Placebo vs the Recommended Treatment Regimen With Intravenous Methylprednisolone in Moderate to Severe Thyroid Eye Disease: A Meta-analysis and Matching-Adjusted Indirect Comparison.	JAMA Ophthalmoll 2022; 140(4): pp.328-35.
Tocilizumab vs. placebo		
Perez-Moreiras et al., 2018	Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, et al. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial.	Am J Ophthalmol 2018;195: pp.181-90.

Source: Table 2-5, pp46 of the submission.
IVMP = IV methylprednisolone; MAIC = matching adjusted indirect comparison.

6.12 The key features of the direct randomised trials are summarised in Table 5 and details of the MAIC and the Bucher ITC are included in Table 6.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Teprotumumab vs placebo						
TEDRV01	88	MC, R, DB 24 weeks	Low	Patients with Graves' disease associated with active TED	Overall responder rate CAS GO-QOL safety	Used
OPTIC	83	MC, R, DB 24 weeks	Low	Patients with Graves' disease associated with moderate-to-severe active TED	Proptosis Overall responder rate CAS Diplopia GO-QOL Safety	Used
OPTIC-X	51	MC, OL, Ex 24 weeks.	High	Subjects with TED who complete the 24-week double-masked treatment period in OPTIC and are proptosis non-responders or who relapsed	Proptosis CAS Diplopia GO-QOL Safety	Not used

Source: Table 2-10, p54 and Table 2-11, pp59-60 of the submission.
CAS = clinical activity score; DB = double blind; Ex = extension study; GO-QOL = Graves' orbitopathy quality of life score; MC = multi-centre; R = randomised; OL = open label; TED = thyroid eye disease.

6.13 Overall, the evaluation considered that the risk of bias in the randomised teprotumumab trials was low and the risk of bias for the extension study was high, due to it being open label. OPTIC-X did maintain blinding regarding what study arm of the OPTIC trial the patients were enrolled in.

Table 6: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Teprotumumab vs IVMP						
Douglas et al., 2022 (Meta-analysis and MAIC)	419 patients for proptosis analysis and 125 patients for diplopia analysis from the IVMP data set. 79 patients from the teprotumumab data set and 83 patients from the placebo data set.[a]	Douglas et al., 2022 carried out an unanchored MAIC comparing teprotumumab to IVMP in active moderate-to-severe TED patients on the outcomes of proptosis and diplopia. The MAIC included TEDRV01 and OPTIC for teprotumumab and 12 studies to inform IVMP.				Used
Teprotumumab vs tocilizumab						
TEDRV01	88	MC, R, DB 24 weeks	Low	Patients with Graves' disease associated with active TED	Proptosis Diplopia	Used
OPTIC	83	MC, R, DB 24 weeks	Low	Patients with Graves' disease associated with moderate-to-severe Active TED	Proptosis Diplopia	Used
Perez-Moreiras et al., 2018 (tocilizumab)	32	DB, R,	Low	Adults with moderate-to-severe corticosteroid-resistant GO	Proptosis Diplopia	Used

Source: Douglas et al., 2022, Perez-Moreiras et al., 2018, Table 2-10, p54 and Table 2-11, pp59-60 of the submission.
DB = double blind; IVMP = IV methylprednisolone; MAIC = matching adjusted indirect comparison; MC = multi-centre; R = randomised; OL = open label; TED = thyroid eye disease.
[a] 493 patients were enrolled in the IVMP studies. Only those with data for proptosis or diplopia were used in the analysis. 83 patients received teprotumumab and 87 patients received placebo in the teprotumumab trials, but some patients were excluded from the MAIC due to missing data.

6.14 As detailed in Table 6, Douglas et al., 2022[14] carried out an unanchored MAIC comparing the efficacy of teprotumumab to IVMP for the treatment of active MS TED based on the outcomes of proptosis and diplopia. The evaluation considered that this study had several issues that may have introduced bias:

- The study was unanchored due to the IVMP studies not having a placebo control arm. As such a common comparator could not be used.
- The researchers only controlled for age, sex, and smoking status when they performed the adjustment. They did not adjust for baseline severity, duration of disease, or comorbid conditions. These omissions could result in confounding. Post-matching baseline characteristics were not provided, and an assessment of the success of matching on non-matched characteristics could not be performed. The transitivity of the studies could not be adequately assessed.

[14] Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, et al. Proptosis and Diplopia Response With Teprotumumab and Placebo vs the Recommended Treatment Regimen With Intravenous Methylprednisolone in Moderate to Severe Thyroid Eye Disease: A Meta-analysis and Matching-Adjusted Indirect Comparison. *JAMA Ophthalmol*. 2022 Apr 1;140(4):328-35.

- The effective sample size of the teprotumumab patients was reduced to 56 patients (from 79) for proptosis and to 44 (from 63) for diplopia. A post-matching comparison for non-adjusted covariates was not presented. The decrease in effective sample size may have increased variability and reduced reliability of the results, as a few heavily weighted patients could disproportionately influence the findings.
- Differences in study design. The teprotumumab trials measured outcomes at 24 weeks while the IVMP trials measured outcomes at 12 weeks. As the symptoms of TED can change over time this may have introduced bias.
- The IVMP studies used in the MAIC did not include MMF and so do not accurately represent the nominated comparator of SoC.

6.15 In addition to the published MAIC from Douglas et al., 2022[16], the submission carried out a supportive, two step, Bucher ITC. This ITC used Salvi et al., 2015[20] to provide data comparing rituximab to IVMP. This was then compared to data from Stan et al., 2015[21] which compared rituximab to placebo. Finally, this was compared to the pooled data from TEDRV01 and OPTIC comparing placebo to teprotumumab. This created a stepped indirect comparison over teprotumumab to IVMP. The evaluation considered that there were several issues that made the results uninformative:

- Differences in population. In Salvi et al., 2015[22] the rituximab arm included a patient population consisting of 93% females and 66% smokers. In Stan et al., 2015[21] the rituximab arm included a patient population consisting of 96% females and 15% smokers. In the combined teprotumumab population from TEDRV01 and OPTIC, 68% were females and 24% were smokers. As these are prognostic factors, the observed outcomes may reflect differences in these baseline characteristics rather than the true effect of the treatments.
- Differences in treatment regimens. The Salvi et al., 2015[22] study initially administered two 1000 mg rituximab doses at a 2-week interval. This was later amended to a single 500 mg infusion. The Stan et al., 2015[21] study administered two rituximab infusions 2 weeks apart.

These factors violate the transitivity assumption requiring that patient populations are sufficiently similar as well as creating inconsistency in the comparison chain resulting in the treatment effect observed in Salvi et al., 2015[22] and Stan et al., 2015[21] not being comparable. As such the evaluation considered that the results from the stepped ITC were not reliable. The PSCR acknowledges that sex and smoking status are prognostic factors, however argued that there was no indication that these were treatment effect modifiers. The PSCR further argued that differences in treatment regimens did not lead to differences in response and maintained that the Bucher ITC was supportive of the MAIC and provided greater certainty to the clinical effect of teprotumumab versus IVMP in the 1L setting.

6.16 The submission also carried out a Bucher ITC comparing teprotumumab to tocilizumab using placebo as a common comparator. The evaluation considered that this comparison also had several issues that may have introduced bias:

- The data for tocilizumab was derived from Perez-Moreiras et al., 2018[13]. This study enrolled patients with TED who were steroid resistant, placing them in the 2L setting. In contrast, the teprotumumab trials only enrolled patients in the 1L setting.
- The tocilizumab study measured efficacy outcomes at 16 weeks compared to 24 weeks in the teprotumumab studies.

6.17 The submission stated that a 2-mm reduction in proptosis and a 1-grade improvement in diplopia have been considered clinically meaningful in prior TED clinical trials. The minimum clinically important difference (MCID) for proptosis is derived from Mourits et al., 1989[15]. In this study, an increase in proptosis of 2 or more millimetres was considered to be a positive sign of disease activity. The MCID for diplopia was derived from Douglas et al., 2022[14], the MAIC that was used to inform the teprotumumab vs. IVMP comparison. However, the Douglas et al., 2022[14] paper does not provide examples of studies where this MCID has been used.

Comparative effectiveness

6.18 The indirect comparisons of teprotumumab to IVMP and tocilizumab relied upon pooled results from the teprotumumab trials TEDRV01 and OPTIC. The pooled results, as derived from Kahaly et al., 2021[16], are presented in Table 7.

[15] Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. *Br J Ophthalmol*. 1989 Aug;73(8):639-44.
[16] Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. *Lancet Diabetes Endocrinol*. 2021 Jun;9(6):360-72.

Table 7: Pooled results from TEDRV01 and OPTIC, 24 weeks.

Outcome Measure	Teprotumumab Group (n=84)	Placebo Group (n=87)	Difference (95% CI)	Relative Risk (95% CI)	p-value
Proptosis Reduction, %, (≥2 mm)	77 (65 of 84)	15 (13 of 87)	**63 (51, 75)**	**5.18 (3.10, 8.66)**	**<0.0001**
Mean Change in Proptosis, mm	-3.14	-0.37	**-2.77 (-3.23, -2.31)**	**-**	**<0.0001**
Diplopia Improvement, % (≥1 grade)	70 (46 of 66)	31 (18 of 59)	**39 (23, 55)**	**2.285 (1.51, 3.47)**	**<0.0001**
Diplopia Resolution, %	53 (35 of 66)	25 (15 of 59)	**28 (12, 44)**	**2.458 (1.52, 3.98)**	**0.0007**
GO-QOL Total Score Improvement, LS Mean (SE)	19.0 (2.1)	6.3 (2.0)	**12.7 (7.02, 18.38)**	**-**	**<0.0001**

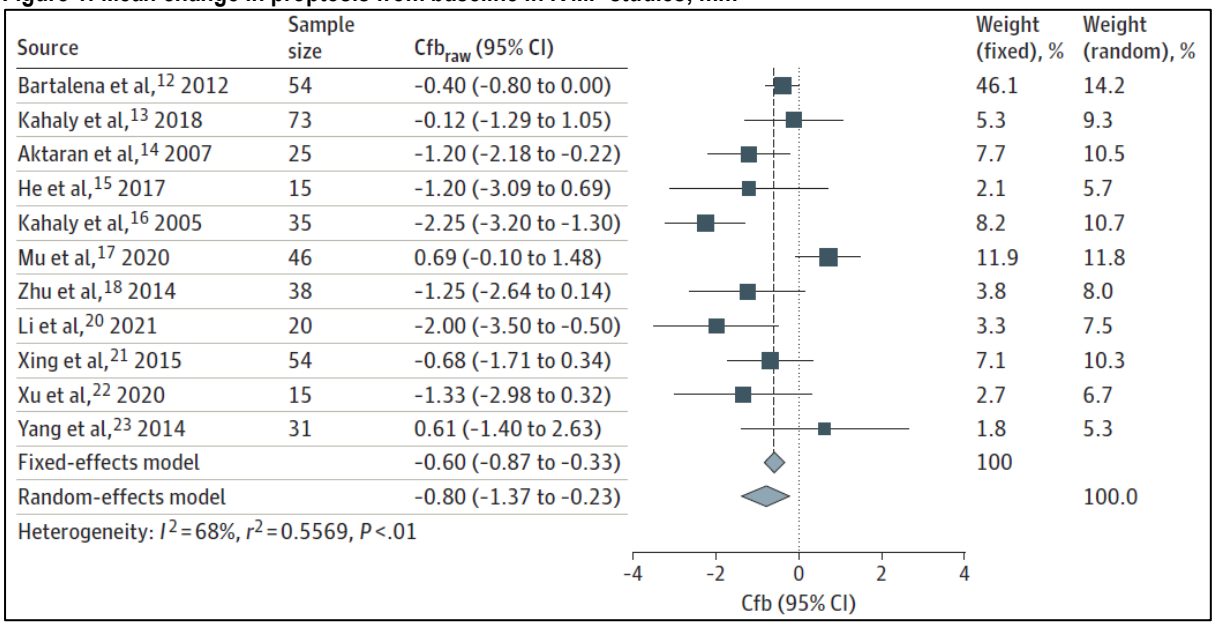
Source: Table 2-55, p123 of the submission
CI = confidence interval; GO-QOL = Graves' orbitopathy quality of life score; LS = least squares; mm = millimetre; RR = relative risk; SE = standard error.
Bold indicates statistically significant results.

6.19 At Week 24, 77% of patients treated with teprotumumab achieved a reduction of at least 2 mm in proptosis compared to 15% in the placebo group (treatment difference 63%, 95% confidence interval [CI]: 51, 75). The mean change in proptosis from baseline at Week 24 was -3.14 mm in the teprotumumab group versus -0.37 mm in the placebo group (difference -2.77 mm, 95% CI: -3.23, -2.31).

6.20 At Week 24, 70% of patients in the teprotumumab group versus 31% in the placebo group showed diplopia improvement by one grade or more (treatment difference 39%, 95% CI: 23, 55). Diplopia resolved in 53% of the teprotumumab group compared to 25% in the placebo group (difference 28%, 95% CI: 12, 44).

6.21 The published MAIC (Douglas et al., 2022[14]) analysis adjusted for baseline differences between the study populations of the IVMP trials and the key teprotumumab studies (OPTIC and TED01RV), by reweighting the individual patient-level data to match the aggregate data from IVMP trials. The mean change in proptosis from baseline in the IVMP studies is shown in Figure 1 and the change in diplopia from baseline in the IVMP studies is shown in Figure 2.

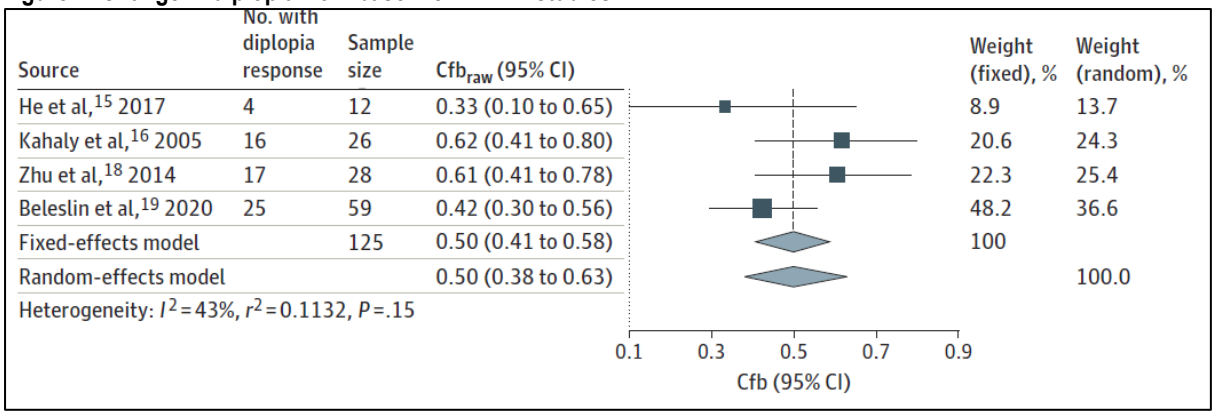
Figure 1: Mean change in proptosis from baseline in IVMP studies, mm



Source: Figure 2-15, p131 of the submission.
Cfb = Change from baseline; Cfbraw = Raw change from baseline; CI = confidence interval

6.22 Mean change from baseline in proptosis was heterogeneous in the IVMP meta-analysis (Figure 1). When combining the 11 identified IVMP studies that reported proptosis, the mean change from baseline was -0.8 mm (95% CI: -1.37, -0.23; random effects model) and -0.60 mm (95% CI: -0.87, -0.33; fixed effects model). The possible causes of the heterogeneity were not discussed.

Figure 2: Change in diplopia from baseline in IVMP studies



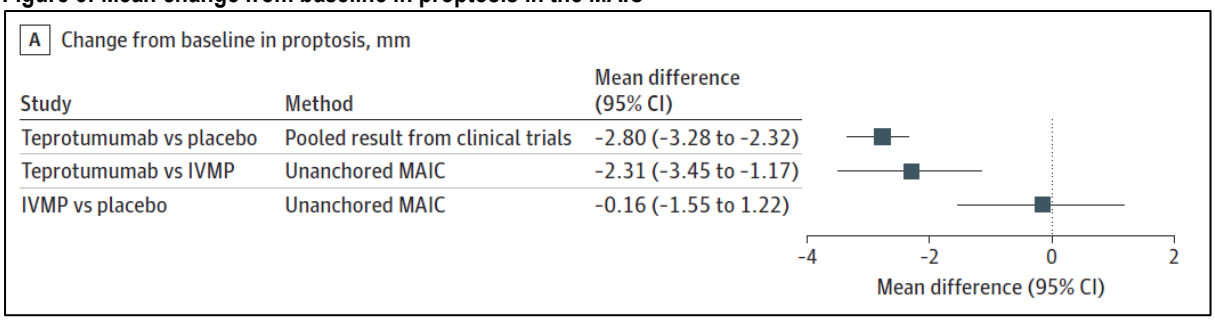
Source: Figure 2-16, p132 of the submission
Cfb = Change from baseline; Cfbraw = Raw change from baseline; CI = confidence interval

6.23 Results in terms of change from baseline for the outcome of diplopia were also heterogeneous in the IVMP studies. When combining the four identified IVMP studies that reported diplopia response, mean response rates were 50% (95% CI: 38%, 63%; random effects model) and 50% (95% CI: 41%, 58%; fixed effects model). Again, the variability across the included studies was not explored.

First-line setting: teprotumumab versus IVMP

6.24 The results of the MAIC comparing the pooled and adjusted teprotumumab results to the pooled IVMP data are reproduced below in Figure 3 and Figure 4.

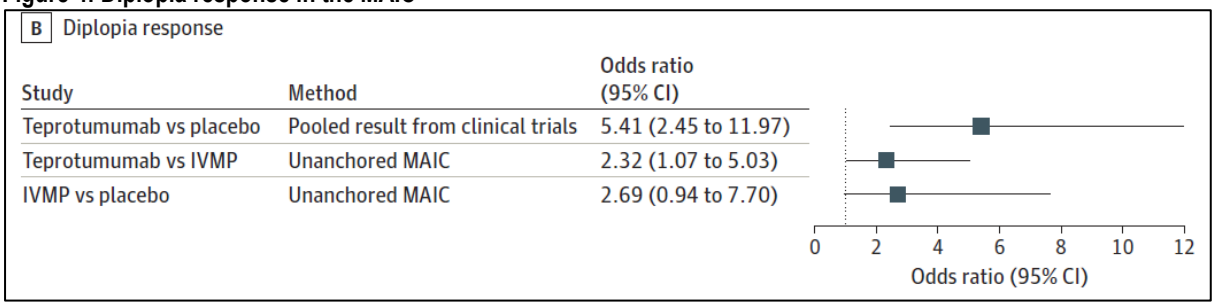
Figure 3: Mean change from baseline in proptosis in the MAIC



Source: Figure 2-17, p133 of the submission.
CI = Confidence interval; IVMP = IV methylprednisolone; MAIC = matching-adjusted indirect comparison.

6.25 Figure 3 shows the mean incremental change from baseline of teprotumumab vs placebo, teprotumumab vs IVMP and IVMP vs placebo in terms of proptosis (mm) as reported by the Douglas et al., 2022[14] MAIC. These results indicated that teprotumumab was associated with a statistically significantly greater change from baseline in proptosis compared with IVMP (mean difference [MD], -2.31 mm, 95% CI: -3.45, -1.17 mm).

Figure 4: Diplopia response in the MAIC



Source: Figure 2-18, p133 of the submission.
CI = Confidence interval; IVMP = IV methylprednisolone; MAIC = matching-adjusted indirect comparison

6.26 The MAIC results for diplopia outcomes showed that teprotumumab was associated with greater odds of diplopia response compared to IVMP, with an odds ratio of 2.32 (95% CI: 1.07, 5.03) (Figure 4).

6.27 The submission also noted that IVMP did not display a statistically significant odds ratio over placebo in either proptosis or diplopia. It is noteworthy that the estimated reduction in proptosis achieved by the pooled IVMP arm was only 0.16 mm greater than that achieved by the matched placebo arm. Therefore, the matched analysis predicted that IVMP (without MMF) had almost no impact on proptosis compared with placebo. The ESC noted that the MAIC concluded that IVMP is no more effective than placebo and therefore considered that it may not provide a reliable basis for comparisons to teprotumumab. The ESC noted that due to the nature of the disease, the benefit of treatment depends on the timing of initiation, with intervention within

6 months (prior to a peak in CAS) generally leading to better patient outcomes[17]. The ESC noted that it wasn't clear at what timepoint patients were treated in the IVMP studies. The ESC considered it is possible that the benefit of IVMP compared to placebo may have been underestimated in the analysis presented due to differences in timing of administration of the treatments.

6.28 The evaluation considered that while these results indicate that teprotumumab is superior to IVMP for the treatment of active MS TED, there are numerous transitivity issues that make the results uncertain:

- As mentioned previously, the lack of a common comparator arm, the limited adjustments for covariates, and the differences in study design likely introduce bias. Furthermore, the reliability of the MAIC is difficult to assess because the MAIC publication did not provide adequate justification for the nominated covariates included for weighting, or a justification for the exclusion of covariates that may impact treatment outcomes (such as disease severity) and did not present the baseline characteristics following weighting.
- Additionally, a significant reduction in effective sample size was seen. 79 patients in the teprotumumab arms had sufficient data to be included in the analysis for proptosis response and 63 patients in the teprotumumab arms had sufficient data to be included in the diplopia response analysis. After weighting, the effective sample size for proptosis dropped to 56 and the effective sample size diplopia dropped to 44. The drop in effective sample size increases variability and reduces reliability of the results, as a few heavily weighted patients could disproportionately influence the findings.
- The heterogeneity observed in the IVMP studies introduces further uncertainty. The studies have different dosing regimens and different study designs with some studies being randomised and others observational. The ESC further noted that the effectiveness of IVMP depends on the dose administered and this was not accounted for in the MAIC[18]. The lack of common control groups in any of the IVMP studies makes it difficult to interpret the heterogeneous results of mean change in proptosis and diplopia response.
- The IVMP studies either had a CAS inclusion criterion of ≥3 (or a median CAS of 4) whereas the teprotumumab trials had a CAS inclusion criterion of ≥4. This may have resulted in there being different levels of disease activity in the enrolled patients. Additionally, heterogeneity is seen in the IVMP trials in the mean

[17] Jose Mario Alves Junior, Wanderley Bernardo, Danilo Villagelin, Effectiveness of Different Treatment Modalities in Initial and Chronic Phases of Thyroid Eye Disease: A Systematic Review With Meta-analysis, The Journal of Clinical Endocrinology & Metabolism, Volume 109, Issue 11, November 2024, Pages 2997–3009

[18] Li H, Yang L, Song Y, Zhao X, Sun C, Zhang L, Zhao H, Pan Y. Comparative effectiveness of different treatment modalities for active, moderate-to-severe Graves' orbitopathy: a systematic review and network meta-analysis. Acta Ophthalmol. 2022 Sep;100(6):e1189-e1198.

duration of TED symptoms (ranging between 4 and 13.6 months) and the mean baseline proptosis (ranging between 17.2 mm and 23.8 mm). These factors may have impacted the observed response to IVMP as longer duration of disease may result in tissue remodelling and patients with smaller baseline proptosis may have less room for improvement.

- The IVMP studies lacked the use of MMF, which is part of the nominated comparator.

6.29 All of these factors mean that the results of the MAIC may not be appropriate to support decision making. The ESC considered the MAIC did not adequately account for the complexity of treatment of TED.

6.30 In addition to the published MAIC from Douglas et al., 2022, the submission carried out a supportive, two step, Bucher ITC. The stepped ITC resulted in a relative risk (RR) of 12.1 (95% CI: 0.82, 178.41) for teprotumumab compared to intermediate dose IVMP and a RR of 18.35 (95% CI: 1.35, 249.5) for teprotumumab compared to high dose IVMP for the outcome of proptosis. For diplopia a RR of 64.93 (95% CI: 5.46, 772.78) was reported to teprotumumab compared to intermediate dose IVMP and a RR of 29.2 (95% CI: 2.64, 322.6) for teprotumumab compared to high dose IVMP. These results suggest that teprotumumab is superior to IVMP in treating proptosis and diplopia. However, it was noted that the RR of proptosis response was 2.34 (0.15, 36.3) when placebo was compared with IVMP (in favour of placebo), and the RR of diplopia response was 20.65 (1.67, 255.50) again in favour of placebo. As noted previously (paragraph 6.15) the evaluation considered the results from the stepped ITC were not reliable.

Second-line setting: teprotumumab versus tocilizumab

6.31 The submission presented a Bucher ITC between teprotumumab and tocilizumab for the second-line treatment of TED using placebo as a common comparator.

6.32 The results of the ITC are presented below with proptosis response shown in Table 8 and diplopia non-response shown in Table 9.

Table 8: Indirect treatment comparison of teprotumumab compared with tocilizumab for proptosis response

Intervention	Comparator	Relative Risk (95% CI)
Placebo	Teprotumumab	**0.19 (0.12, 0.33)**
Placebo	Tocilizumab	**0.50 (0.30, 0.85)**
Teprotumumab	Tocilizumab	**2.6 (1.25, 5.41)**
Tocilizumab	Teprotumumab	**0.38 (0.18, 0.8)**

Source: Table 2-77, p143 of the submission`
CI = confidence interval
Bold indicates statistically significant results

6.33 Using the pooled proptosis response in the teprotumumab pooled arm with the response data from Perez-Moreiras et al. 2018[19], the submission estimated the relative risk of proptosis response was 2.6 (95% CI: 1.25, 5.41) in favour of teprotumumab.

Table 9: Indirect comparison in diplopia non-response comparing teprotumumab with tocilizumab

Intervention	Comparator	Relative Risk (95% CI)
Placebo	Teprotumumab	**2.27 (1.66, 3.10)**
Placebo	Tocilizumab	1.07 (0.94, 1.22)
Teprotumumab	Tocilizumab	**0.47 (0.34, 0.66)**

Source: Table 2-85, p146 of the submission
CI = confidence interval
Bold indicates statistically significant results

6.34 The Perez-Moreiras et. al. 2018 study reported only one tocilizumab patient with diplopia response, compared with no placebo patients. As a comparative analysis could not be conducted using a zero count, a non-responder analysis was conducted.

6.35 No difference in non-responders was seen when comparing tocilizumab with placebo (relative risk [RR]: 0.93, 95% CI: 0.82, 1.07). In contrast, placebo patients were more likely to be non-responders when compared with teprotumumab patients (RR: 0.44, 95% CI: 0.32, 0.6).

6.36 Using the non-responder values, the submission calculated that patients treated with tocilizumab were twice as likely to be non-responders compared with patients treated with teprotumumab (RR: 0.47, 95% CI: 0.34, 0.66), indicating that teprotumumab was statistically superior to tocilizumab for diplopia response.

6.37 Although the Bucher ITC comparing teprotumumab to tocilizumab indicates that teprotumumab had superior efficacy, the evaluation considered that the results should be interpreted with caution. As mentioned previously, the patients in the teprotumumab trials were all treated in the 1L setting whereas the patients in the tocilizumab trials are all patients in the 2L setting after displaying resistance to steroid treatment. It is uncertain what impact this population difference will have on the results. The ESC further noted that the results in the teprotumumab trials were measured at 24 weeks, whereas the tocilizumab results were measured at week 16 and that the time to treatment also varied across the teprotumumab studies (~6 months) versus the tocilizumab studies (~1 year).

Comparative harms

6.38 A summary of the safety results from the key teprotumumab trials is presented in Table 10.

[19] Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, et al. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. Am J Ophthalmol. 2018 Nov;195:181-90.

Table 10: Summary of key adverse events in the teprotumumab trials

Participants with	TED01RV trial		OPTIC trial			
	Tep (N =43)	PBO (N =44)	Tep (N=41) [At Week 24]	PBO (N=42) [At Week 24]	Tep (N=36) [At Follow-up]	PBO (N=4) [At Follow-up]
≥1 TEAE (Any), n(%)	32 (74.4)	32 (72.7)	35 (85.4)	29 (69.0)	26 (72.2)	3 (75.0)
≥1 treatment-related TEAE, n(%)	24 (55.8)	18 (40.9)	23 (56.1)	11 (26.2)	7 (19.4)	0
≥1 serious TEAE, n(%)	5 (11.6)	1 (2.3)	2 (4.9)	1 (2.4)	2 (5.6)	0
≥1 treatment-related serious TEAE, n(%)	NR	NR	1 (2.4)	0	0	0
≥1 TEAE with an intensity of severe or higher, n(%)	4 (9.3)	0	1 (2.4)	1 (2.4)	3 (8.3)	0
≥1 TEAE leading to interruption of study drug, n(%)	NR	NR	0	0	NR	NR
≥1 TEAE leading to permanent withdrawal of study drug, n(%)	5 (11.6)	1 (2.3)	1 (2.4)	1 (2.4)	NR	NR
≥1 treatment-related TEAE leading to permanent withdrawal of study drug, n(%)	NR	NR	1 (2.4)	0	NR	NR
≥1 TEAE leading to study discontinuation, n(%)	NR	NR	1 (2.4)	1 (2.4)	0	0
≥1 treatment-related TEAE leading to study discontinuation, n(%)	NR	NR	1 (2.4)	0	0	0
TEAEs leading to death, n(%)	0	0	0	0	0	0

Source: Table 2-40, p110 of the submission.
NR = not reported; PBO = placebo; TEAE = treatment emergent adverse event; Tep = teprotumumab.

6.39 In the TEDRV01 study, the percentage of subjects with treatment emergent adverse events (TEAEs) was similar in the teprotumumab and placebo groups: 32 (74.4%) and 32 (72.7%), respectively. The most common TEAEs in the teprotumumab group (>5% and greater than placebo) were nausea (18.6%), muscle spasms (18.6%), diarrhea (14.0%), hyperglycaemia (11.6%), alopecia (7.0%), dry skin (7.0%), dysgeusia (7.0%), headache (7.0%), paraesthesia (7.0%), and weight decrease (7.0%).

6.40 In the OPTIC trial, most subjects in both treatment groups experienced at least 1 TEAE (85.4% teprotumumab and 69.0% placebo) with a greater proportion being reported in the teprotumumab arm. TEAEs that occurred more commonly in the teprotumumab group compared to the placebo group (≥5.0% difference) included muscle spasms (31.7% versus 9.5%), alopecia (19.5% versus 11.9%), nausea (14.6% versus 9.5%), fatigue (12.2% versus 2.4%), dysgeusia (9.8% versus 0), dry skin (9.8% versus 0), dizziness (7.3% versus 0) and amenorrhoea (7.3% versus 0).

6.41 The ESC noted that hearing impairment was deemed a TEAE of special interest and that 4 (9.8%) subjects in the teprotumumab group in the OPTIC trial had TEAEs related

to hearing impairment versus none in the placebo group. The specific TEAE varied with deafness, hypoacusis, and tinnitus reported.

6.42 In the OPTIC-X trial the overall incidence of adverse events was comparable between the OPTIC-X arms (previous teprotumumab treated and previous placebo treated patients) and the teprotumumab arm of the OPTIC trial. The only adverse event which was different was muscle spasms in the previous placebo treated patients (18/37, 49%) compared with teprotumumab treated OPTIC patients (13/41, 32%).

6.43 Although no deaths were reported from teprotumumab, a total of 5 (11.6%) subjects in the teprotumumab arm of the TEDRV01 trial reported serious AEs (SAEs). The reported SAEs were diarrhoea, inflammatory bowel disease, Escherichia sepsis, Hashimoto's encephalopathy, and urinary retention. None of the SAEs were reported in more than one patient. All SAEs in the teprotumumab group were deemed “serious” because hospitalisation occurred. These results indicate that teprotumumab has inferior safety to placebo.

6.44 The submission did not present a formal comparison of safety between teprotumumab and IVMP or tocilizumab.

6.45 The submission presented a summary of life-threatening complications associated with IVMP used for the treatment of Graves’ orbitopathy (Table 11).

Table 11: Life-threatening complications of high doses of intravenous methylprednisolone for treatment of Graves' orbitopathy

Organ system	Report	Complication	Dose of IVMP
Hepatic complications	Marino et al., 2000[20]	Acute liver failure (7 out of 800 patients, including 3 lethal cases)	3.0–24.0 g
	Weissel and Hauff 2000[21]	Acute liver failure (lethal, 1 patient)	15.0 g
	Salvi et al., 2004[22]	Acute liver failure (1 patient)	5.5 g
Cardiovascular complications	Owecki et al., 2006[23]	Severe hypertension leading to myocardial infarction (1 patient)	5.0 g
	Gursoy et al., 2006[24]	Severe hypertension leading to acute hear failure without myocardial infarction (1 patient)	2.0 g
	Lendorf et al., 2009[25]	Myocardial infarction (1 out of 49 patients) Angina pectoris (2 out of 49 patients) Ischemic stroke (lethal, 1 out of 49 patients) Pulmonary embolism (lethal, 1 out of 49 patients)	2.0–5.0 g

Source: Table 2-91, p157 of the submission.
IVMP = IV methylprednisolone

6.46 The submission stated that IVMP for TED can be life-threatening if used in high doses. Additionally, minor adverse events caused by IVMP for TED have been reported to include Cushingoid appearance, weight gain, gastrointestinal symptoms, insomnia, hypertension, glucose intolerance, urinary tract infection, and palpitation. Reported serious adverse events include hepatotoxicity, major depression, psychosis, new onset diabetes mellitus, severe infection, profound muscle weakness, fulminant liver failure, cardiovascular events, and death.

6.47 The evidence presented does not allow for a formal safety comparison between teprotumumab and IVMP. The safety profile of IVMP is well established and is known to be associated with serious and life-threatening adverse events. However, without a formal comparison, a definitive assessment of the safety claim cannot be made as IVMP has been used in a much greater number of patients, increasing the likelihood of adverse events being reported. Furthermore, the safety reports associated with IVMP come from less controlled conditions than what is found in a clinical trial, introducing further confounding.

[20] Marinó, M. *et al.* Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 14, 403-406 (2004)
[21] Weissel, M. & Hauff, W. Fatal liver failure after high-dose glucocorticoid pulse therapy in a patient with severe thyroid eye disease. *Thyroid* 10, 521-521 (2000).
[22] Salvi, M. *et al.* Onset of autoimmune hepatitis during intravenous steroid therapy for thyroid-associated ophthalmopathy in a patient with Hashimoto's thyroiditis: case report. *Thyroid* 14, 631-634 (2004).
[23] Owecki, M. & Sowiński, J. Acute myocardial infarction during high-dose methylprednisolone therapy for Graves' ophthalmopathy. *Pharmacy World and Science* 28, 73-75 (2006).
[24] Gursoy, A., Cesur, M., Erdogan, M. F., Çorapcioglu, D. & Kamel, N. New-onset acute heart failure after intravenous glucocorticoid pulse therapy in a patient with Graves' ophthalmopathy. *Endocrine* 29, 513-516 (2006).
[25] Lendorf, M. E., Rasmussen, A. K., Fledelius, H. C. & Feldt-Rasmussen, U. Cardiovascular and cerebrovascular events in temporal relationship to intravenous glucocorticoid pulse therapy in patients with severe endocrine ophthalmopathy. *Thyroid* 19, 1431-1433 (2009).

6.48 Table 12 presents AEs associated with tocilizumab as reported in Perez-Moreiras et al. 2018[13]. The Perez-Moreiras et al. 2018[13] paper reported total adverse events (AEs) rather than the number or proportion of patients who experienced an AE. Additionally, the paper reported AEs at both week 16 and week 40. This makes a comparison to teprotumumab difficult.

Table 12: Adverse events of tocilizumab compared with placebo for active moderate-to-severe, treatment resistant thyroid eye disease.

	Week 16		Week 40	
	Tocilizumab (n=15)	Placebo (n=17)	Tocilizumab (n=15)	Placebo (n=17)
Total AEs	43	19	58	33
Infections	12	5	17	7
Respiratory tract	6	2	3	1
Gastroenteritis	2	1	3	1
Urinary tract infections	2	0	2	0
Headache	9	2	11	4
Anaemia	0	3	0	3
Ocular symptoms (pain)	0	0	2	3
Hypercholesterolemia	2	0	3	1
Neutropenia (Grade I)	1	0	1	0
Thrombocytopenia (Grade I)	1	0	1	0
Patients with >1 AEs, n	9	4	12	7
Total SAEs, n	2	0	2	0

Source: Table 2-91, pp157-158 of the submission.
AEs = adverse events; SAEs = serious adverse event.

6.49 Given the lack of a formal comparison of safety and the differences in reporting between Perez-Moreiras et al. 2018[13] and the teprotumumab studies, the evaluation considered that it was not possible to conclude if the evidence provided supports the claim of non-inferior safety.

Benefits/harms

6.50 A summary of the comparative benefits for teprotumumab versus placebo is presented in Table 13. Due to the identified issues with the indirect comparison versus IVMP, this comparison is not presented in Table 13. As the submission did not present a formal comparison of safety, a summary of harms could not be presented. Key safety concerns for teprotumumab are presented above.

Table 13: Summary of comparative benefits for teprotumumab and placebo

Trial	Teprotumumab n/N	PBO n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Teprotumumab	PBO	
Benefits						
Diplopia improvement						
Pooled teprotumumab trials	46/66	18/59	**2.29 (1.51, 3.47)**	70	31	**0.39 (0.23, 0.55)**
Change from baseline: proptosis						
	Teprotumumab		**PBO**		**Mean difference*: Teprotumumab vs. PBO (95% CI)**	
	N	**Mean Δ baseline (proptosis)**	**N**	**Mean Δ baseline (proptosis)**		
Pooled teprotumumab trials	84	-3.14 mm	87	-0.37 mm	**-2.77 mm (-3.23, -2.31)**	

Source: Table 2-26, p95 and Table 2-55, p123 of the submission, and Figure 2-17, p133, and Figure 2-18, p133 of the submission.
CI = confidence interval; OR = odd ratio; PBO = placebo; RD = risk difference; RR = risk ratio; SD = standard deviation
* The results for the teprotumumab trial were reported at 24 weeks and for placebo at week 12 (Douglas et al, 2022)
Bold = statistically significant.

6.51 On the basis of pooled results from the teprotumumab trials TEDRV01 and OPTIC, as derived from Kahaly et al., 2021[26] and presented by the submission, patients with MS TED treated with teprotumumab in comparison to placebo, over 24 weeks would on average experience:

- Approximately a 2.77 mm greater reduction of proptosis.

For every 100 patients with MS TED treated with teprotumumab in comparison to placebo, over 24 weeks:

- Approximately 39 more patients would experience improvement in diplopia of ≥1 grade.

Clinical claim

6.52 The submission described teprotumumab as superior in terms of effectiveness compared to SoC comprising of IVMP with or without MMF in the 1L setting and tocilizumab in the 2L setting.

6.53 The ESC considered the claim of superior efficacy for teprotumumab over IVMP with or without MMF was uncertain. The presented MAIC had a number of issues that resulted in considerable uncertainty in the estimate of effectiveness of teprotumumab vs IVMP. The MAIC results for diplopia outcomes showed that teprotumumab was associated with greater odds of diplopia response compared to IVMP (OR: 2.32, 95% CI: 1.07, 5.03) and that teprotumumab was associated with a statistically significantly greater change from baseline in proptosis compared with IVMP (MD, -2.31 mm; 95% CI: -3.45, -1.17). Although the results of the MAIC indicated that teprotumumab was

[26] Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. *Lancet Diabetes Endocrinol*. 2021 Jun;9(6):360-72.

superior to IVMP for the treatment of active MS TED, the lack of a common comparator arm, the limited adjustments for covariates, the reduction in effective sample size, and the differences in study design introduced bias. Additionally, none of the IVMP studies included MMF as a treatment and so this comparison was not representative of SoC in Australia. Furthermore, the ESC noted that the unanchored MAIC concluded that IVMP is no more effective than placebo and that this may have been due to the timing of treatment as well as the IVMP dose. The ESC therefore considered that it may not provide a reliable basis for comparisons to teprotumumab. Overall, the ESC considered that the MAIC was unreliable and did not adequately account for the complexity of treatment of thyroid eye disease.

6.54 The ESC noted that the PSCR stated that there was one comparative study comparing IVMP+MMF with IVMP (Kahaly et. al. 2018) and that this study showed that the response to treatment at 12 weeks was not statistically different between the two arms (OR: 1.76, 95% CI: 0.92, 3.39; p=0.089). The PSCR argued that as there is no evidence of a statistically significant difference between IVMP and IVMP+MMF, the comparison between IVMP and teprotumumab is reflective of any comparison between IVMP+MMF and teprotumumab. The PSCR stated that this was reflective of the ETA/ATA guidelines (Burch et. al. 2022) which also state there is no difference between IVMP and IVMP+MMF. The ESC considered that the comparative effect of teprotumumab versus IVMP+MMF and the added benefit of MMF was difficult to quantify with the available evidence. The ESC noted that a network meta-analysis (NMA) suggested there may be a small effect[27].

6.55 The ESC noted that the relative benefit of treatment appeared to vary according to the clinical outcome measured and methodological approach. Based on the Li 2022[28] network meta-analysis, the benefit of teprotumumab over IVMP in the 1L setting appeared to relate to change in proptosis, while the Alves Junior 2024 meta-analysis[29] (for treatment <6 months of disease duration) suggested the benefit was driven by diplopia. In both these analyses no difference in change in CAS was demonstrated between these two therapies. The Pre-PBAC response noted that the lack of a difference in CAS reduction between teprotumumab and IVMP is not unexpected, as IVMP is an effective anti-inflammatory treatment. The Response stated that CAS is a composite outcome which includes changes in pain, swelling (chemosis), redness, bloodshot eyes (conjunctival injection), and inflammation of the caruncle or plica. The

[27] Li H, Yang L, Song Y, Zhao X, Sun C, Zhang L, Zhao H, Pan Y. Comparative effectiveness of different treatment modalities for active, moderate-to-severe Graves' orbitopathy: a systematic review and network meta-analysis. Acta Ophthalmol. 2022 Sep;100(6):e1189-e1198. doi: 10.1111/aos.15074. Epub 2021 Dec 16. PMID: 34918472.

[28] Li H, Yang L, Song Y, Zhao X, Sun C, Zhang L, Zhao H, Pan Y. Comparative effectiveness of different treatment modalities for active, moderate-to-severe Graves' orbitopathy: a systematic review and network meta-analysis. Acta Ophthalmol. 2022 Sep;100(6):e1189-e1198. doi: 10.1111/aos.15074. Epub 2021 Dec 16. PMID: 34918472.

[29] Jose Mario Alves Junior, Wanderley Bernardo, Danilo Villagelin, Effectiveness of Different Treatment Modalities in Initial and Chronic Phases of Thyroid Eye Disease: A Systematic Review With Meta-analysis, The Journal of Clinical Endocrinology & Metabolism, Volume 109, Issue 11, November 2024, Pages 2997–3009

Response also stated that while CAS is an established tool used to assess disease activity, it is not applicable for a comparative efficacy analysis because CAS assigns equal weight to each component of the score, which is not reflective of their clinical value to patients or clinicians. The Response also stated that there were a number of limitations associated with the Li et al (2022) and Alves Junior (2024) studies, however noted that the results of both studies demonstrated that teprotumumab is superior, in terms of proptosis reduction and diplopia improvement, compared to IVMP in the 1L setting.

6.56 The evaluation and the ESC considered the claim of superior efficacy for teprotumumab over tocilizumab in the 2L setting was not adequately supported. The submission used a Bucher ITC to compare teprotumumab to tocilizumab using placebo as a common comparator. Using this method the submission estimated the relative risk of proptosis response was 2.6 (95% CI: 1.25, 5.41) in favour of teprotumumab, and estimated that patients treated with tocilizumab are twice as likely to be non-responders compared with patients treated with teprotumumab (0.47, 95% CI: 0.34, 0.66) in terms of diplopia. However, all patients in the teprotumumab trial received teprotumumab as a 1L treatment while patients in the tocilizumab trial received the study drug as second-line treatment, subsequent to steroid resistance. Additionally, the results in the teprotumumab trials were measured at 24 weeks, whereas the tocilizumab results were measured at 16 weeks. The ESC further noted that the time to treatment also varied across the teprotumumab studies (~6 months) versus the tocilizumab studies (~1 year). The ESC considered that these issues made the results unreliable.

6.57 The ESC noted that the submission had also presented data reported by Men et al. 2024 and Toro Tobon et al. 2023[30] to support the use of teprotumumab in the 2L setting (also see paragraph 3.5). The ESC noted that although the analysis by Toro Tobon et al. 2023 did not report differences between the steroid naïve and steroid experienced patients treated with teprotumumab, that the comparison was limited due to the small numbers of patients in each arm, as well as the inherent bias associated with case-control studies. The ESC noted that patients with recalcitrant disease treated with teprotumumab in Men et al. 2024[31] had similar outcomes to those reported in 1L studies, however, the ESC considered that overall there was insufficient data available to support using the efficacy derived from 1L studies as a proxy for 2L use of teprotumumab in an indirect comparison to 2L tocilizumab.

6.58 The pre-PBAC response acknowledged there was methodological limitations associated with the comparative evidence presented in the submission, however

[30] Toro-Tobon D, Rachmasari KN, Bradley EA, Wagner LH, Tooley AA, Stokken JK, Stan MN. Medical Therapy in Patients with Moderate to Severe, Steroid-Resistant, Thyroid Eye Disease. *Thyroid*. 2023 Oct;33(10):1237-44.

[31] Men, C. J., Amarikwa, L., Sears, C., Shinder, R., Clauss, K., Ugradar, S., Cockerham, K., Wester, S., Douglas, R., & Kossler, A. (2024) Teprotumumab for the Treatment of Recalcitrant Thyroid Eye Disease. *Ophthalmic Plast Reconstr Surg* 40(4), 276-285.

noted that the consistency of the findings favouring teprotumumab across multiple analyses were collectively supportive of the clinical claim in the 1L setting. The Response acknowledged that the clinical evidence in the 2L setting was less robust; however, again noted multiple methodologies demonstrated a consistently significant benefit for teprotumumab over tocilizumab.

6.59 The submission described teprotumumab as non-inferior (with the strong possibility of superiority) in terms of safety compared to IVMP with or without MMF in the 1L setting and non-inferior in terms of safety compared to tocilizumab in the 2L setting. The PSCR further clarified that the safety profiles of teprotumumab are 'non-inferior but different'. The ESC considered this claim was not adequately supported as the submission did not present a formal comparison of safety between teprotumumab and IVMP or tocilizumab. The submission correctly stated that the safety of IVMP is well known and that the use of high dose IVMP, as seen in TED, is associated with a variety of serious AEs, including fatal AEs. However, without a formal comparison, a definitive assessment of the safety claim cannot be made as IVMP has been used in a much greater number of patients, increasing the likelihood of adverse events being reported. Furthermore, the safety reports associated with IVMP come from less controlled conditions than what is found in a clinical trial, introducing further confounding. The ESC also noted that there were significant safety concerns associated with teprotumumab including permanent hearing impairment as week as other common adverse events. Likewise, no formal comparison of safety was made between teprotumumab and tocilizumab and so the ESC considered the claim of non-inferior safety was not supported. The ESC further considered that the possibility that teprotumumab has inferior safety compared to tocilizumab could not excluded.

6.60 Overall, the PBAC considered that while there was significant uncertainty related to the ITCs presented, the totality of the available evidence suggests that the claim of superior efficacy of teprotumumab versus IVMP in the 1L setting and tocilizumab in the 2L setting was likely reasonable. However, the PBAC considered that the magnitude of treatment effect of teprotumumab versus SoC was uncertain due to the substantial transitivity violations across the comparisons.

6.61 The PBAC noted that while there were significant safety concerns related to teprotumumab, including permanent hearing impairment, that IVMP with or without MMF and tocilizumab were also associated with significant safety risks. Overall, the PBAC considered that the claim of non-inferior comparative safety of teprotumumab versus the current SoC therapies to be uncertain, but likely reasonable.

Economic analysis

6.62 Three comparisons were presented in the submission's economic analysis:

- Teprotumumab vs IVMP in the 1L setting
- Teprotumumab vs IVMP + MMF in the 1L setting
- Teprotumumab vs tocilizumab in the 2L setting

Neither comparison in the 1L setting reflects current practice, where MMF would be used in patients with minimal response after three infusions of IVMP, and orbital radiotherapy at 12 weeks if there is ongoing severe disease.[11] The evaluation considered that due to the lack of clinical evidence presented in the submission to support the comparison of teprotumumab to IVMP + MMF, or the use of teprotumumab in the 2L setting, these cost-effectiveness analyses were not likely to be informative for PBAC decision-making. Therefore, the analyses presented herein focus on 1L teprotumumab therapy relative to IVMP.

6.63 The submission presented a stepped economic evaluation based on the unanchored MAIC (Douglas et al. 2022)[14] that compared pooled data from the teprotumumab TED01RV and OPTIC trials to IVMP in patients with active MS TED. The type of economic evaluation presented was a cost-utility analysis.

6.64 Table 14 summarises the key components of the economic evaluation.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Three analyses were presented: (1L) teprotumumab vs IVMP; (1L) teprotumumab vs IVMP + MMF; and 2L teprotumumab vs tocilizumab.
Time horizon	Lifetime (47 years) in the model base case vs. 72 weeks follow-up from teprotumumab trials.
Outcomes	QALYs, based on improved symptom severity.
Methods used to generate results	Markov cohort expected value.
Health states	Nine health states: SPND, LPND, SPID, LPID, SPCD, LPCD, Surgery, Post-surgery, Dead.
Cycle length	6 weeks
Transition probabilities	Treatment phase (cycles 1–4/week 1–24): time-varying transitions of symptom improvement and relapse were informed by pooled data from TED01RV and OPTIC, with the IVMP treatment effect, relative to placebo, derived from an unanchored MAIC (Douglas et al. 2022). Teprotumumab discontinuation (8.4% over the 24-week treatment course) was also based on the pooled teprotumumab trial data, with IVMP discontinuation (2.7% over the 12-week treatment course) based on Kahaly et al. (2018)[32]. Extrapolation (cycles 5–12/week 24–72): transitions of relapse were informed by follow-up data up to 72 weeks (based on overall relapse rate of 30% [OPTIC] following teprotumumab; and 50% [Salvi et al. 2015[33]] following IVMP). Long-term extrapolation (cycles 13+/week 72+): TED symptoms were assumed to be stable. Rehabilitative surgery was assumed as a one-off in cycle 26 (i.e. beginning of inactive phase), where use varied by symptom severity (SPND/SPID: 5.0%; LPND: 38.1%; LPID: 41.3%; SPCD/LPCD: 43.8%), and was informed from clinician opinion. All patients alive in the Surgery health state in cycle 56 were assumed to transition to the Post-surgery health state. Across all phases, patients remain at-risk of death based on ABS Life Tables (2020–2022).
Health related quality of life	TTO methodology was used to elicit utility scores for TED health state vignettes from a sample of the general US population (SPND: 0.60; LPND: 0.46; SPID: 0.52; LPID: 0.43; SPCD: 0.34; LPCD: 0.30) (Smith et al. 2023)[34]. Utilities for the Surgery and Post-surgery health states were assumed based on the lowest (0.30) and median (0.43) active MS TED health state values, respectively. Utility decrements were included for Grade ≥3 AEs which occurred in ≥5% of patients and for IV administration.

Source: Adapted from Table3–1, pp167–168 of the submission.

1L = first-line; 2L = second-line; AEs = adverse events; IV = intravenous; IVMP = intravenous methylprednisolone; LPCD = large proptosis with constant diplopia; LPID = large proptosis with intermittent/inconstant diplopia; LPND = large proptosis with no diplopia; MAIC = matching-adjusted indirect comparison; MMF = mycophenolate mofetil; MS TED = moderate-to-severe thyroid eye disease; QALY = quality-adjusted life year; QoL = quality-of-life; SPCD = small proptosis with constant diplopia; SPID = small proptosis with intermittent/inconstant diplopia; SPND = small proptosis with no diplopia; TED = thyroid eye disease; TTO = time trade-off.

6.65 The structure of the economic model is presented in Figure 5. Patients entering the model were distributed across six health states reflecting levels of proptosis (small and large) and diplopia (none; intermittent or inconstant; and constant)[35]. Additional health states (Surgery and Post-surgery) were included in the model to reflect rehabilitative surgery (implemented across the cohort as a one-off at three years) to

[32] Kahaly GJ, Riedl M, Konig J, Pitz S, Ponto K, Diana T, et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018 Apr;6(4):287-98.

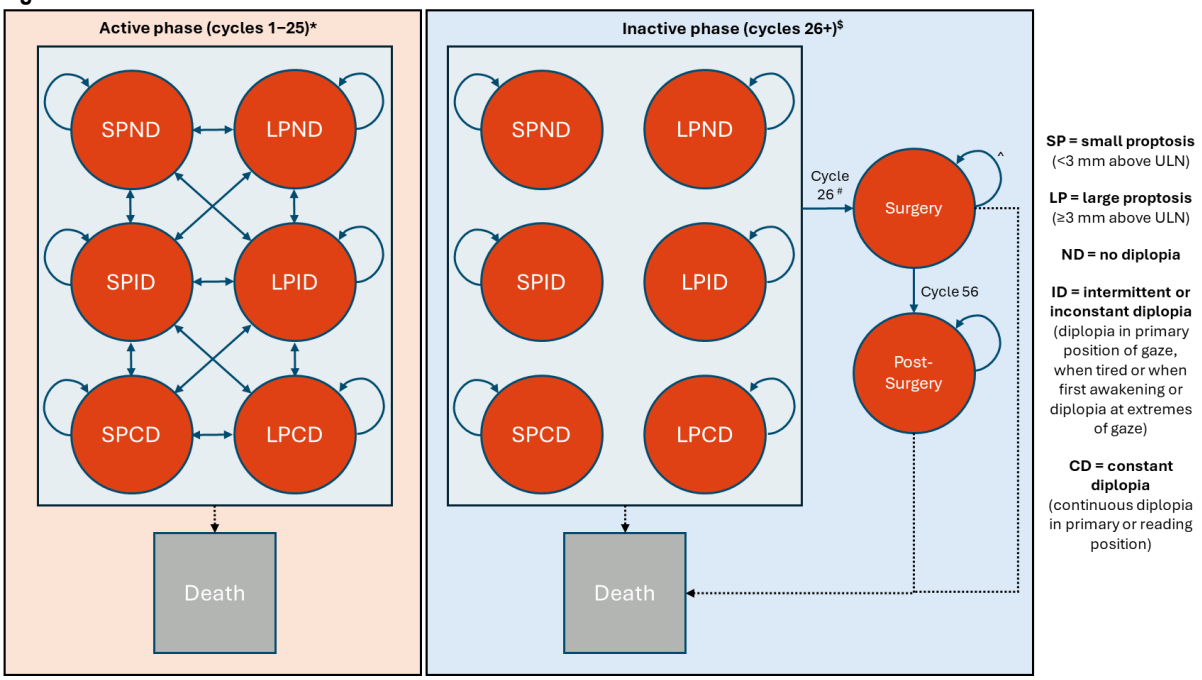
[33] Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015 Feb;100(2):422-31.

[34] Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015 Feb;100(2):422-31.

[35] Subjective diplopia score used in the trial

correct the sequelae of active disease once TED has become inactive (inflammation has subsided). The evaluation considered that given that a number of the model assumptions could be accounted for using a simpler decision analytic structure – i.e. no changes in TED symptoms after 72 weeks and that surgery is assumed in all patients who require it at the same time (para 6.73) – the use of a more complex Markov model structure was not well justified.

Figure 5: Structure of the economic model



Source: Constructed during the evaluation based on Figure 3.2–1, p176 of the submission.
LPCD = large proptosis with constant diplopia; LPID = large proptosis with intermittent/inconstant diplopia; LPND = large proptosis with no diplopia; SPCD = small proptosis with constant diplopia; SPID = small proptosis with intermittent/inconstant diplopia; SPND = small proptosis with no diplopia; TED = thyroid eye disease; ULN = upper limit of normal for race and sex.
* Not all transitions between TED health states in the active phase have been depicted nor are all allowed throughout the phase due to limitations of data and other model assumptions. Symptom improvements are modelled only to week 24 (cycle 4 – duration of comparative trial data), whereas relapses are modelled up to week 72 (cycle 12 – extent of observed data). After week 72, TED symptoms are assumed to stabilise and patients remain in that health state until the end of the active phase.
$ In the Inactive phase (3 years after model entry), unless patients receive rehabilitative surgery – assumed to occur only in Cycle 26 – the level of TED symptoms is assumed to remain unchanged throughout the model time horizon (i.e. no transitions between TED symptom health states). All patients who remain alive in the Surgery health state in cycle 56 (approx. 3.5 years after rehabilitative surgery) are assumed to transition to the Post-surgery health state.
# Transitions to the Surgery health state vary by TED symptom health state (SPND/SPID: 5.0%; LPND: 38.1%; LPID: 41.3%; SPCD/LPCD: 43.8%)
^ No patients are assumed to remain in the Surgery health state in cycle 56

6.66 The following issues were noted by the evaluation regarding the model structure, which likely limit the reliability of the model for decision-making purposes:

- The submission has not adequately supported that the TED symptom health states chosen reflect meaningful differences in QoL. Significant differences in health state utility were not observed between all (vignette-based) health states in a time trade-off (TTO) study in a sample of the general US population (n = 111)

(Smith et al. 2023)[36], nor were clinically meaningful differences observed in QoL between these health states at baseline in the teprotumumab trials (Smith et al. 2024)[37]. The vignette study considered that changes between states may be difficult to detect (e.g. from intermittent/inconstant diplopia to no diplopia) or that symptoms have similar impacts on daily life.[36] While resource use for disease management and the proportion of patients who require rehabilitative surgery were also assumed to vary by health state, these differences were informed by expert opinion.

- Based on the utility values applied to the TED symptom health states, these represent active MS TED, with limited distinction modelled between the active (characterised by presence of inflammation) and inactive (once inflammation has subsided) phases. This was not likely to be reasonable as active disease is associated with pain, grittiness, chemosis and photophobia, which may subside in the inactive phase, and lead to improvement in QoL.
- The model did not account for other relevant aspects of disease, such as progression to sight-threatening TED (which requires urgent surgery during the active phase of disease), resolution of TED symptoms to mild disease nor reactivation after active disease has subsided and the health states as modelled represent heterogeneous patients (e.g. TED symptom health states represent patients on 1L treatment, patients on 2L treatment, patients who have relapsed, etc. and the Surgery/Post-surgery health states represent patients with mixed TED symptoms). The evaluation considered that it may be reasonable to collapse some of the health states (e.g. large proptosis with no diplopia [LPND], small proptosis with intermittent/inconstant diplopia [SPID] and large proptosis with intermittent/inconstant diplopia [LPID]; and small proptosis with constant diplopia [SPCD] and large proptosis with constant diplopia [LPCD]), which would increase the observed data available to inform each of the probabilities of transitioning in the model.

The ESC considered that the health states likely reflected clinically meaningful differences for MS TED patients, however there was insufficient data to reliably inform a complex model with numerous transition probabilities. The ESC noted that a number of transition probabilities in the transition matrix appeared anomalous, likely due to being derived from small patient numbers. The ESC considered, that in the context of limited data, it may be more appropriate to aggregate health states to improve the reliability of the model. Overall, the ESC considered that the model was likely not reliable for decision making.

[36] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility Assessment of Moderate to Severe Thyroid Eye Disease Health States. JAMA Ophthalmol. 2023 Feb 1;141(2):159-66.

[37] Smith TJ, Cockerham K, Barretto N, Hirst A, Oliver L, Enstone A, et al. Bridging and Validation of the Specific Graves Ophthalmopathy Quality of Life Questionnaire With Health State Utility Values. Endocr Pract. 2024 May;30(5):470-5.

6.67 The Pre-PBAC response maintained that the economic model appropriately reflected TED as a biphasic disease where the active phase includes 1-2 lines of first-line treatment followed by an inactive phase and surgical procedures. Active disease can be considered in 3 phases itself (active treatment, subsequent regression or relapse, and stable disease). Late reactivation of disease is uncommon and hence was not incorporated, as it would have added unnecessary complexity to the model.

6.68 As there are no explicit stopping or continuing criteria proposed for the listing of teprotumumab and given that there is some evidence for use of teprotumumab as retreatment – due to lack of response, relapse during the active phase, or reactivation following inactive disease – these uses should have been included in the model. A scenario was presented in the submission exploring the impact of teprotumumab retreatment on the incremental cost-effectiveness ratio (ICER), however as described in para 6.87, the assumptions applied were highly uncertain and likely underestimate this impact.

6.69 A summary of the model and treatment effects by disease phase is presented in Table 15. The modelled results are driven by a greater reduction in symptom severity following teprotumumab than IVMP. The magnitude of this reduction is highly uncertain given the evidence presented against IVMP and the durability of this effect beyond the trial data is unknown. The reduction in symptom severity was assumed to persist beyond the trial data (i.e. no worsening of proptosis or diplopia assumed in Cycles 13+) and is effectively used as a surrogate for use of rehabilitative surgery and subsequent treatment. No evidence was available to support a difference in use of rehabilitative surgeries following teprotumumab treatment due to reduced symptom severity, nor presented to support the transformation of symptom severity into surgeries required. It is unclear whether teprotumumab temporarily modulates the disease or whether it results in true disease modification.[38]

[38] Hwang CJ, Rebollo NP, Mechels KB, Perry JD. Reactivation After Teprotumumab Treatment for Active Thyroid Eye Disease. Am J Ophthalmol. 2024 Jul;263:152-9.

Table 15: Summary of the model, as it relates to phases of disease, and the modelled effect of treatment

Phase summary	Model approach	Modelled benefit of teprotumumab
Active Inflammation present and symptoms can worsen. Treatment is required, including urgent surgery if symptoms become sight-threatening, which can improve symptoms. Patients who discontinue or do not respond to 1L treatment or relapse may require further treatment.	In Cycles 1–4 (weeks 1–24), patients can transition between all of the TED symptom health states (i.e. symptoms can improve or deteriorate). If symptoms such as proptosis (≥3mm ULN) and/or constant diplopia persist after completion of 1L treatment, patients receive 2L therapy (cost impact only). In Cycles 5–12 (weeks 24–72), transitions reflecting a relapse (i.e. deterioration of symptoms) are allowed between TED symptom health states.[a] However, additional treatment was not modelled in patients who relapsed. Once patients experienced one relapse, they are not at-risk of experiencing further relapses. No further transitions between TED states were assumed after Cycle 13. No difference was assumed across treatment arms in terms of surgery due to sight-threatening TED, or duration of active disease.	Teprotumumab was associated with reduced symptom severity (i.e. more transitions to less severe health states), which was associated with improved QoL and lower costs of disease management. Reduced symptom severity following teprotumumab led to a reduction in 2L treatment required. Teprotumumab was associated with a lower relapse rate in Cycles 5–12 (30% vs 50%), which further reduces the relative symptom severity by the end of the active phase.
Inactive Sequelae of inflammation remain (e.g. symptoms of proptosis and/or diplopia), although symptoms of local inflammation have subsided. Rehabilitative surgery can occur to correct residual symptoms, though may not be able to restore pre-morbid appearance.	The inactive phase is modelled from Cycle 26 (i.e. 3 years after model entry), based on the timing in the model of rehabilitative surgery (implemented as a one-off in a proportion of patients in Cycle 26). No difference is assumed in the utility applied for the TED symptom health states to reflect this disease phase. Lower disease management costs were applied in Cycle 36+ which may reflect lower disease management costs in the inactive phase, though the delay (i.e. from Cycle 26 to Cycle 36) in application of the reduced cost was not explained. The need for and number of rehabilitative surgeries are assumed to be directly related to symptom severity. Patients remain in the Surgery health state for 3 years (i.e. from Cycle 26 to Cycle 55) and then transition to the Post-surgery health state.	With reduced symptom severity at the end of the active phase, a modelled benefit of teprotumumab was a reduction in the proportion of patients requiring rehabilitative surgery (model output: 21% vs 34%), and in those who require surgery, a reduction in the number of procedures performed.
Reactivation Reactivation ≥6 months of disease stability of TED symptoms has been reported in the literature.[39,40] These may require further treatment.	No reactivations of disease were modelled.	Teprotumumab was implicitly assumed to have no impact on the incidence of relapse in Cycle 13+ or reactivations in the inactive phase. Teprotumumab retreatment may occur as this use is allowed within the proposed PBS listing, and as there is evidence supporting this use.

Source: Constructed during the evaluation based on Section 3 of the submission. 1L = first-line; 2L = second-line; QALY = quality-adjusted life year; QoL = quality-of-life; TED = thyroid eye disease; ULN = upper limit of normal

[a] For diplopia, one-step relapse only has been assumed – e.g. only transition from ND to ID, not to CD

[39] Patel P, Khandji J, Kazim M. Recurrent Thyroid Eye Disease. Ophthalmic Plast Reconstr Surg. 2015 Nov-Dec;31(6):445-8.

[40] Selva D, Chen C, King G. Late reactivation of thyroid orbitopathy. Clin Exp Ophthalmol. 2004 Feb;32(1):46-50.

6.70 In the first four model cycles (24 weeks), TED symptoms could improve or relapse in response to treatment. Transition probabilities for teprotumumab, including treatment discontinuation (2.18% per model cycle, based on 8.4% of patients discontinuing over the 24-week treatment period), were based on the pooled individual patient-level data (IPD) from the TED01RV and OPTIC trials. As shown in Figure 5, there were 36 possible transitions for each model cycle between the TED symptom health states. Given that the number of observations used to inform these transitions was relatively small (maximum observations in the teprotumumab arm was 80), each of the individual transitions are likely to be associated with a high degree of uncertainty with small differences likely having a large impact on the modelled probabilities. As noted in para 6.66, it may have been reasonable to collapse some of the health states, increasing the observed data available to inform transition probabilities.

6.71 Transition probabilities for IVMP were based on the pooled IPD data from the placebo arms of the TED01RV and OPTIC trials. In cycles 1 and 2, pseudo-IPD for the change in proptosis symptoms were generated by applying the mean difference from baseline in proptosis for IVMP relative to placebo at 12 weeks, based on the Douglas et al.[14] MAIC (-0.16 mm). As discussed in para 6.53, the MAIC presented was associated with considerable uncertainty and the resulting estimates likely prone to bias. The ICER was moderately sensitive to changes in the mean difference applied (see Table 19). For changes in diplopia symptoms, an RR[41] (2.09) was applied to transition probabilities related to improving diplopia response for placebo from the pooled set. The RR was applied in cycle 1 only (i.e. to week 6), which was not consistent with the data from the MAIC[14] which reported improved response to 12 weeks. Further, the placebo data used in cycle 2 were derived from changes in diplopia response between week 6 and week 24. These approaches were not justified in the submission. It may be more appropriate to use placebo data from week 6 to week 12 in cycle 2 and apply the RR. The ICER was moderately sensitive to this change (see Table 19).

6.72 Between model cycles 5–12 (weeks 24–72), in patients who completed 1L treatment, TED symptoms could continue to relapse. Once patients had relapsed during this phase, no further changes in TED symptoms were assumed. This assumption was not justified and resulted in patients who experience worsening in one symptom not being at risk of subsequent worsening in the other symptom – for example, a patient who transitions from small proptosis with no diplopia (SPND) to SPID would no longer be at risk of developing large proptosis – which may not be reasonable. This also meant that patients with no diplopia could relapse to intermittent/inconstant diplopia but would not be at further risk of developing constant diplopia. Relapse rates of 30% and 50% were assumed in the teprotumumab and IVMP model arms, respectively, based

[41] The observed probability of response with placebo was converted into the odds of improving response. The OR reported (2.69) was used to calculate the odds of response with IVMP, which was then converted into a probability of response. The ratio of the probabilities was used to derive the RR.

on teprotumumab data to 72 weeks (OPTIC) and IVMP data to 52 weeks.[42] No comparative evidence was presented to support this difference, noting that the ICER was sensitive to the difference across model arms assumed (see Table 19). Loss of response was not specifically reported in Salvi et al. 2015[42]; this was rather assumed based on the lack or limited durable response observed to week 52 following IVMP treatment (1/16 patients was observed to have a reduction in proptosis of ≥2 mm by week 24, which was maintained at week 52). The evaluation concluded that given that differences in relapse rates across model arms applied in cycles 5–12 is a driver of the cost-effectiveness, in the absence of reliable evidence demonstrating a difference in relapse rates across treatment arms following treatment completion, a more conservative approach should be adopted.

6.73 Beyond cycle 13 (week 72+), no further changes in TED symptoms were assumed, and patients were modelled to receive rehabilitative surgery, at one time if required, in cycle 26. The assumption that active disease would subside (and so be eligible for rehabilitative surgery) across all patients at the same time may be simplistic in the context of a Markov model structure. The proportion of patients who received rehabilitative surgery (and the number of surgeries required) was assumed to vary by TED symptom health state based on a survey of UK clinicians, which was also used to inform the time spent in this state (30 cycles, i.e. 3.5 years), before transitioning to the Post-surgery health state. No empirical data were available to validate clinician estimates. Therefore, incremental costs and outcomes related to differences in rehabilitative surgery are associated with considerable uncertainty.

6.74 Patients who discontinued treatment were assumed to receive 2L therapy, based on a mix of tocilizumab (60%), rituximab (5%) and radiotherapy (35%). Transition probabilities following 2L treatment were based on treatment effectiveness data for tocilizumab (relative to placebo)[13] applied to placebo data from the TED01RV and OPTIC trials (i.e. in the 1L setting). It may not be reasonable to assume outcomes for 2L therapy derived from those in the 1L setting, and this may overestimate the effect of 2L treatment. In cycles 3 and 4, observed data from placebo-treated patients were used without adjustment, significance of the tocilizumab treatment effect was not maintained to week 40.[13] As the effect of subsequent treatment was modelled based on time in the model, rather than time in the health state, the benefit for use of subsequent treatment was limited to cycle 2 and so applied only to patients who discontinued treatment in cycle 1.

[42] Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015 Feb;100(2):422-31.

6.75 The cost of subsequent treatment was also applied in patients who remained in the large proptosis and/or constant diplopia health states after completing 1L treatment. However, subsequent treatment was not assumed to have any impact on modelled outcomes in these patients. The evaluation considered that this was not reasonable, and favoured teprotumumab as fewer patients were assumed to receive subsequent treatment due to symptom persistence after completing 1L treatment (20.6% vs 62.6%).

6.76 The submission adopted a lifetime time horizon. The ESC noted that this was substantially longer than the duration of evidence available for teprotumumab (up to 72 weeks). The submission stated that a lifetime time horizon would be reasonable given the long-term nature of the disease and that diplopia and proptosis symptoms persist in inactive disease. Given the uncertainties related to the lasting effect of teprotumumab and the relationship between symptom severity and the need for and outcomes of rehabilitative surgery, the use of a lifetime time horizon is not appropriate and is associated with considerable uncertainty. This may be reduced by applying a shorter time horizon. In the context of non-infectious intermediate, posterior or panuveitis, where benefits were expected to accrue over the patient's remaining life expectancy, the PBAC considered a 10-year time horizon appropriate as the majority of ocular complications occur within 2–5 years (para 7.14, adalimumab public summary document [PSD], March 2017 PBAC Meeting). The ESC considered that a 10-year time horizon would also be appropriate for teprotumumab. The ESC noted that a substantial increase (93%) in the ICER was observed when the time horizon was reduced to 10 years (see Table 19).

6.77 All health state utility values used in the economic model were either presented in or derived from Smith et al. 2023[36]. As described in para 6.66, this study used TTO methodology to elicit utility scores for TED health state vignettes from a sample of the general US population (n = 111). As the utilities generated are not directly provided by patients living in the health states, the utilities represent preferences for a vignette, which can differ from the health status of actual patients with the condition.[43] The ESC considered that the reported values were very low, ranging from 0.30–0.60 for the most (i.e. LPCD) to least (i.e. SPND) severe health states. The ESC considered that the low utilities lacked face validity, for example, small proptosis no diplopia (SPND) a utility value of 0.60 implies a willingness to sacrifice 40% of life expectancy to prevent SPND. The ESC considered that this was likely not reasonable. The ESC noted that the ICER was observed to be particularly sensitive to changes in the SPND utility value, and moderately sensitive to changes in the LPID and LPCD utilities (see Table 19). Given these uncertainties, estimates outside of the ranges tested could be plausible. Utility decrements were included for Grade ≥3 AEs which occurred in ≥5% of patients and for IV administration. No justification was provided for including only those AEs which

[43] Matza LS, Stewart KD, Lloyd AJ, Rowen D, Brazier JE. Vignette-Based Utilities: Usefulness, Limitations, and Methodological Recommendations. Value Health. 2021 Jun;24(6):812-21.

occurred in ≥5% of patients. AEs of special interest associated with teprotumumab, such as hearing loss, were therefore not included. The ESC considered that this was not reasonable.

6.78 For the Surgery and Post-surgery health states, the submission assumed that values from Smith et al. 2023[36] (i.e. active MS TED) would apply. The lowest utility was assumed for the Surgery health state (0.30), and the median value, excluding SPND, was used for the Post-surgery health state (0.43). The evaluation considered that this was not reasonable given that the rationale for surgery is to correct disfigurement and improve QoL in affected patients[44] and there are likely utility differences between active and inactive TED. As modelled, only some health states (SPCD and LPCD) would result in improvement in QoL following surgery – and this would occur only once patients transition to the Post-surgery state (3.5 years after surgery). Given that more patients in the comparator arm were assumed to receive rehabilitative surgeries, the use of lower-than-expected utility values is likely to bias in favour of teprotumumab. Alternate values were presented (though not used) in the submission's economic file (Surgery: 0.38; Post-surgery: 0.50)[45]. The ICER was sensitive to changes in the utility values applied following surgery (see Table 19).

6.79 The pre-PBAC Response maintained that the utility values applied to the base case of the economic model were appropriate and emphasised that TED is a disabling and disfiguring condition that has significant impact on quality of life. The Response noted that if differences between the utility values for each health state were kept the same (as reported by Smith et al. 2023), but the absolute values were higher by any arbitrary amount, then there is no change in ICER.

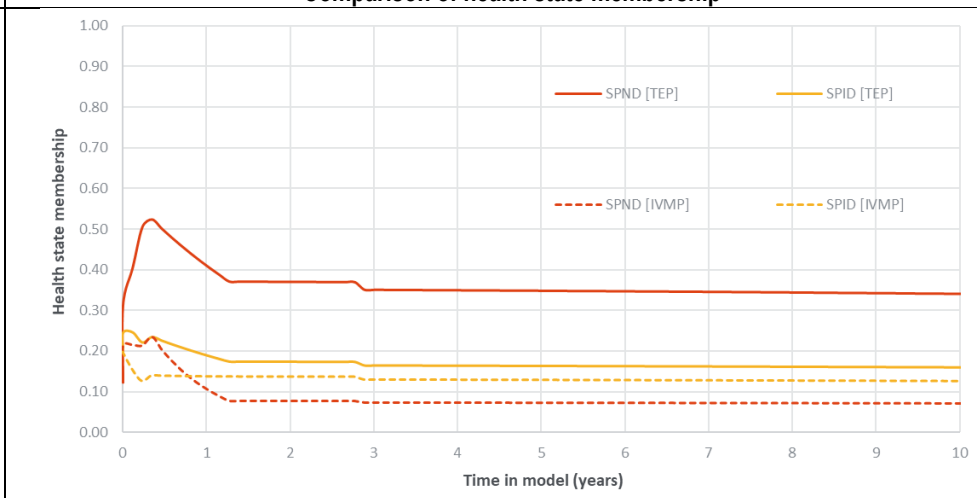
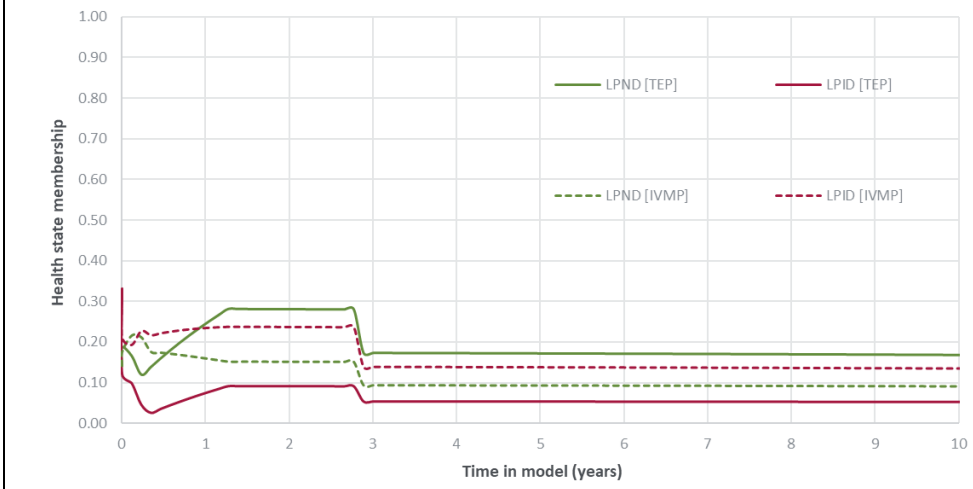
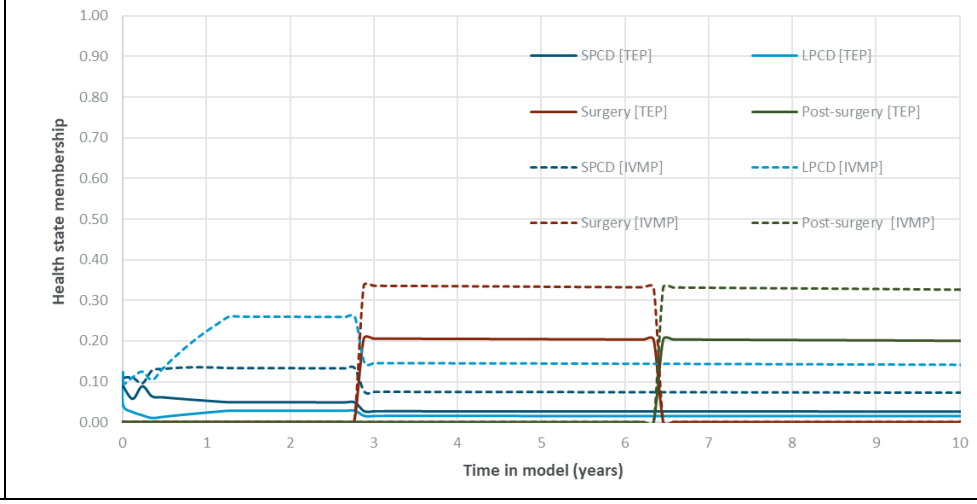
6.80 Figures depicting a comparison of health state membership between the teprotumumab and IVMP arms over the first 10 years in the model are presented in Table 16. Thereafter, the proportions of patients in TED symptom health states and in the Post-surgery health state reduced gradually up to the end of the time horizon (47 years) due to background mortality. These demonstrate the shift in time spent in health states associated with more severe symptoms (constant diplopia – SPCD or LPCD, or where symptoms in both attributes are observed – LPID), which are associated with poorer QoL, to health states associated with less symptoms and higher QoL (e.g. no diplopia – SPND and LPND, or small proptosis – SPID) and the reduction in the time spent in the Surgery and Post-surgery health states. These graphs show that patients treated with teprotumumab spend substantially more time in the model in the no diplopia (ND) health states (particularly in the SPND health state), whereas patients treated with IVMP spend the most time in the Surgery and Post-surgery

[44] Woo T, Li C, Ganesananthan S, Rajendram R, Uddin J, Lee RWJ, et al. The Effect of Ophthalmic Surgery for Graves' Orbitopathy on Quality of Life: A Systematic Review and Meta-Analysis. Thyroid. 2022 Feb;32(2):177-87.

[45] average of LPND, LPID, SPCD and LPCD utility values for Surgery; and average SPND, LPND, SPID and LPID utility values for Post-surgery.

states. Prior to surgery, IVMP patients are predominantly assigned to the large proptosis states, in particular LPCD and LPID.

Table 16: Health state membership over the first 10 years in the model, by health state

	Comparison of health state membership
A. SPND and SPID health states	
B. LPND and LPID health states	
C. SPCD, LPCD, Surgery and Post-surgery health states	

Source: Constructed during the evaluation from the 'Attachment 17 Tepezza Economic model.xlsb' file included in the submission.

IVMP = intravenous methylprednisolone; LPCD = large proptosis with constant diplopia; LPID = large proptosis with intermittent/inconstant diplopia; LPND = large proptosis with no diplopia; SPCD = small proptosis with constant diplopia; SPID = small proptosis with intermittent/inconstant diplopia; SPND = small proptosis with no diplopia; TEP = teprotumumab.

6.81 The average number of teprotumumab vials assumed per patient for initial dosing (10 mg/kg) was 2.10 vials and 3.58 vials for subsequent dosing (20 mg/kg), based on IPD of patient weight from all patients enrolled in the OPTIC trial. Given that transition probabilities in the model were derived from pooled data, IPD of patient weight from the pooled data may be more appropriate (2.12 vials for initial; 3.61 vials for subsequent), however the ICER was not sensitive to this difference. The cost per infusion, including administration, was adjusted for compliance (91.57%), based on the proportion of patients in the pooled data set who completed the teprotumumab treatment course (i.e. 8 doses). The evaluation considered that this was not appropriate as this same data was used to inform the teprotumumab discontinuation rate (para 6.70) and so the model has double-counted the impact of teprotumumab discontinuation. The ICER was sensitive to increasing the compliance applied to 100% (11% increase, see Table 19).

6.82 A summary of the key drivers of the model is presented in Table 17.

Table 17: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted] [1]/QALY gained
Time horizon	Lifetime (47 years). Given the uncertainties related to the lasting effect of teprotumumab and the relationship between symptom severity and the need for and outcomes of rehabilitative surgery, the use of a lifetime time horizon is likely not appropriate and is associated with considerable uncertainty.	High, favours teprotumumab. Use of a 10-year time horizon increased the ICER to $[redacted] [2]/QALY gained.
IVMP relapse rate, cycles 5–12	50% based on the assumption that the benefit in proptosis would revert to the baseline, less an additional 15% to account for natural history progression, as IVMP was not shown to provide any or limited durable response by Week 52. This resulted in a higher relapse rate applied following IVMP than following teprotumumab (30%). No comparative evidence was presented to support this difference.	High, favours teprotumumab. Assuming a 30% relapse rate in cycles 5–12 following IVMP (i.e. same as applied for teprotumumab) increased the ICER to $[redacted] [3] /QALY gained.
SPND health state utility	0.60 derived from a vignette-based TTO study, Smith et al. 2023[46]. The reported values from this study were noted to be low (0.30−0.60).	High, in both directions. Use of the lower 95% CI estimate (0.54), increased the ICER to $[redacted] [3]/QALY gained, and use of the upper 95% CI estimate (0.67) reduced the ICER to $[redacted] [1]/QALY gained.
Surgery and Post-surgery utility values	Surgery: 0.30 (lowest TED symptom utility reported in Smith et al. 2023); and Post-surgery: 0.43 (median utility of health states, excluding SPND, reported in Smith et al. 2023).	High, favours teprotumumab. Assuming Post-surgery utility as for (active MS) SPND (0.60) increased the ICER to $[redacted] [4] /QALY gained.

[46] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility Assessment of Moderate to Severe Thyroid Eye Disease Health States. JAMA Ophthalmol. 2023 Feb 1;141(2):159-66.

Description	Method/Value	Impact Base case: $[redacted] [1]/QALY gained
		Using other alternate utility values: 0.38 for Surgery and 0.50 for Post-surgery, increased the ICER to $[redacted] [4]/QALY.
Proportion receiving rehabilitative surgery	SPND/SPID: 5.0%; LPND: 38.1%; LPID: 41.3%; SPCD/LPCD: 43.8% applied once-off to the proportion of patients in the respective health states in Cycle 26.	Moderate-high, in both directions. Assuming that 43.8% of patients require surgery (maintaining that the number of surgeries varies by health state) increases the ICER to $[redacted] [3]/QALY gained. Decreasing the proportion across all states to 5% decreased the ICER to $[redacted] [1]/QALY gained.
IVMP treatment effect on proptosis versus PBO	Mean difference in proptosis (-0.16 mm) based on the MAIC conducted by Douglas et al. (2022)[47]. The MAIC presented was associated with considerable uncertainty and the resulting estimates likely prone to bias.	Moderate-high, direction unknown. The ICER ranged from $[redacted] [1]/QALY gained to $[redacted] [4]/QALY gained when the upper (1.22 mm) and lower (-1.55 mm) limits of the 95% CI for the mean difference in proptosis were used
IVMP treatment effect on diplopia response versus PBO	OR of diplopia response (2.69) based on the MAIC conducted by Douglas et al. (2022) was applied in cycle 1 only (i.e. week 1−6). This was not consistent with the data from the MAIC which reported improved response to 12 weeks.	Moderate, favours teprotumumab. Applying the OR in cycle 1 and 2 (week 1−12) increased the ICER to $[redacted] [4]/QALY gained.
TEP compliance	91.6% based on the proportion of patients in the pooled data set who completed the teprotumumab treatment course (i.e. 8 doses). This was not appropriate as this same data was used to inform the teprotumumab discontinuation rate and so the model has double-counted the impact of teprotumumab discontinuation.	Moderate, favours teprotumumab. Increasing compliance to 100% increased the ICER to $[redacted] [4]/QALY gained.

Source: Constructed during the evaluation from the 'Attachment 17 Tepezza Economic model.xlsb' file included in the submission.
CI = confidence interval; ICER = incremental cost-effectiveness ratio; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; MS = moderate-to-severe; OR = odds ratio; PBO = placebo; QALY = quality-adjusted life year; SPND = small proptosis with no diplopia; TED = thyroid eye disease; TEP = teprotumumab; TTO = time trade-off.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$135,000 to < $155,000*
[3] *$95,000 to < $115,000*
[4] *$75,000 to < $95,000*

6.83 The submission presented a stepped economic evaluation; however, the final step included a number of modelling assumptions: extrapolation of symptom severity to the end of the active phase, transformation of symptom severity into rehabilitative surgeries required, transformation of life-years gained across modelled health states into QALYs and extrapolation over a lifetime time horizon. During the evaluation a revised analysis was conducted to incorporate these modelling assumptions in a stepped manner to allow the results to be presented sequentially before and after these key translational steps (Table 18).

[47] Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, et al. Proptosis and Diplopia Response With Teprotumumab and Placebo vs the Recommended Treatment Regimen With Intravenous Methylprednisolone in Moderate to Severe Thyroid Eye Disease: A Meta-analysis and Matching-Adjusted Indirect Comparison. JAMA Ophthalmol. 2022 Apr 1;140(4):328-35.

6.84 Given the uncertainty related to the magnitude and lasting effect of symptom improvement with teprotumumab compared to IVMP and the reliability of the model to translate the available clinical evidence into long-term health and quality of life projections, alternate analyses may provide a more reliable basis for decision-making, noting that the PBAC previously accepted an ICER per disfigurement-free responder (para 7.10, vismodegib PSD, March 2016 PBAC Meeting). Alternate cost per responder analyses are presented in the stepped generation of results below.

Table 18: Results of the stepped economic evaluation

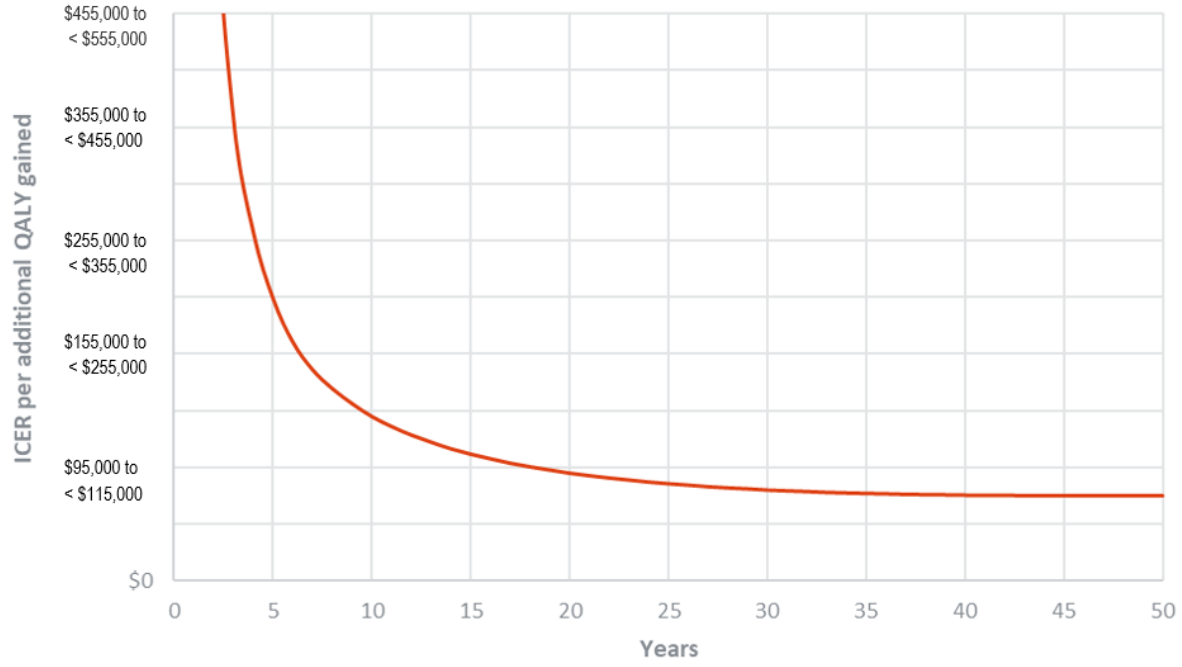
Step and component	TEP	IVMP	Increment
Step 1: Trial-based costs and outcomes (24 weeks) Treatment costs (including administration) assumed all patients completed the respective treatment course, with no adjustment for compliance. Use of TEP was based on IPD of patient weight in the pooled TED01RV and OPTIC trials. Transitions of improvement and relapse were informed by the pooled data, with a treatment effect for IVMP, relative to placebo, derived from the MAIC conducted by Douglas et al. (2022). Average health state membership across the 24-week period was used to determine the proportion of patients in the SPND or SPID health state.			
Costs	$[redacted]	$5,699	$[redacted]
Patients in the SPND or SPID health state	67.4%	37.4%	30.0%
Incremental cost per additional patient in SPND or SPID health state			$[redacted] 1
Step 2: Time horizon extended to 72 weeks Costs unchanged from Step 1. Between week 24–72, transitions of relapse were informed by follow-up data up to 72 weeks (OPTIC, Salvi et al. 2015). Average health state membership across the 72-week period was used to determine the proportion of patients in the SPND and SPID health states.			
Costs	$[redacted]	$5,699	$[redacted]
Patients in the SPND or SPID health state	64.6%	30.5%	34.2%
Incremental cost per additional patient in SPND or SPID health state			$[redacted] 1
Step 3: Inclusion of subsequent treatment cost Subsequent treatment cost of $3,349.50[a] applied to patients who had discontinued treatment, or those in the LPND, LPID, SPCD and LPCD health states at the end of treatment. The proportions of patients treated were derived from average health state membership across the 1L treatment phase (24 weeks) in those who discontinued, or who were in the applicable health states. Subsequent treatment was not assumed to have any impact on symptoms in this step.			
Costs	$[redacted]	$7,826	$[redacted]
Patients in the SPND or SPID health state	64.6%	30.5%	34.2%
Incremental cost per additional patient in SPND or SPID health state			$[redacted] 1
Step 4: Model-based analysis, extrapolated to cycle 26 (to reflect duration of active phase [3 years]) Modelled costs of treatment (including administration) (where TEP use was based on IPD of patient weight from the OPTIC trial, and included adjustment for discontinuation and compliance), subsequent treatment ($3,404.84 per patient) [a], health state management and AEs were included. Discounting of costs included. Average health state membership across the 26 cycles was used to determine the proportion of patients in the SPND and SPID health states.			
Costs	$[redacted]	$16,681	$[redacted]
Patients in the SPND or SPID health state	59.1%	25.6%	33.6%
Incremental cost per additional patient in SPND or SPID health state			$[redacted] 2
Step 5: Estimation of rehabilitative surgeries avoided Based on health state membership at the end of the active phase of disease (i.e. 3 years), a one-off proportion of patients are assumed to require rehabilitative surgery (SPND/SPID: 5.0%; LPND: 38.1%; LPID: 41.3%; SPCD/LPCD: 43.8%). The type and number of surgeries required (and therefore cost of surgery) was also assumed to vary by health state.			
Costs	$[redacted]	$26,941	$[redacted]
Patients in the SPND or SPID health state	59.1%	25.6%	33.6%
Incremental cost per additional patient in SPND or SPID health state			$[redacted] 2
Patients requiring rehabilitative surgery	20.6%	33.7%	−13.1%
Incremental cost per rehabilitative surgery avoided			$[redacted] 3
Step 6: Transformation into QALYs			
Costs	$[redacted]	$26,941	$[redacted]
QALYs	1.4633	1.2117	0.2516
Incremental cost/extra QALY gained			$[redacted] 1
Step 7: Extrapolation over lifetime time horizon (47 years)			
Costs	$[redacted]	$46,932	$[redacted]
QALYs	8.103	6.817	1.286
Incremental cost/extra QALY gained			**$[redacted] 4**

Source: Adapted from Table 3−38, p215 of the submission.

1L = first-line; AE = adverse event; IPD = individual patient-level data; IVMP = intravenous methylprednisolone; LPCD = large proptosis with constant diplopia; LPID = large proptosis with intermittent/inconstant diplopia; LPND = large proptosis with no diplopia; MAIC = matching-adjusted indirect comparison; QALY = quality-adjusted life year; SPCD = small proptosis with constant diplopia; SPID = small proptosis with intermittent/inconstant diplopia; SPND = small proptosis with no diplopia; TEP = teprotumumab.
[a] The cost of subsequent treatment applied in Step 3 ($3,349.50) differed to Step 4 ($3,404.84), based on a different course cost of rituximab applied ($1,353.36 and $1,785.72, respectively). The rituximab cost applied in Step 3 was hardcoded into the model and the basis for this could not be determined during the evaluation.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$255,000 to < $355,000*
[3] *$755,000 to < $855,000*
[4] *$55,000 to < $75,000*

6.85 The ESC noted that the step that had the most impact on the ICER was the extrapolation to the lifetime time horizon. Given issues regarding the lasting effect of teprotumumab treatment in terms of reducing symptom severity beyond the trial data and the relationship between symptom severity and use and outcomes of rehabilitative surgery required, the use of a lifetime time horizon is not appropriate and is associated with uncertainty which may be reduced by applying a shorter time horizon. Figure 6 provides a summary of the ICER ($/QALY gained) over the time horizon of the model.

Figure 6: Trace of the ICER ($/QALY) over the time horizon of the model



Source: Constructed during the evaluation from the 'Attachment 17 Tepezza Economic model.xlsb' file included in the submission.
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

6.86 Key univariate sensitivity analyses presented in the submission and conducted during the evaluation for key areas of uncertainty identified are presented in Table 19. The ICER was observed to be most sensitive to the time horizon; health state utility values for SPND, LPCD and LPID; treatment effect of IVMP and IVMP relapse rates in cycles 5–12; and assumptions regarding the Surgery and Post-surgery health states (proportion who receive surgery and utility values).

6.87 The submission presented a scenario analysis exploring the impact of teprotumumab retreatment, which was associated with a small increase in the ICER. In this scenario, following teprotumumab the only subsequent treatment modelled was teprotumumab in a proportion of patients in cycle 13 (26% of patients with large proptosis, based on OPTIC-X[48]). No subsequent treatment was assumed in patients who had discontinued while on teprotumumab nor in those patients who otherwise received subsequent treatment in the base case (i.e. patients in SPCD health state and the remaining 74% of patients with large proptosis). The impact of retreatment on outcomes was applied in cycle 17 (i.e. end of retreatment course) as a 13% probability of transitioning from large to small proptosis. This was based on a 50% proptosis response rate reported in OPTIC-X[49], applied to the proportion of patients with large proptosis who received retreatment (i.e. 26%). No change in diplopia response was assumed, nor were any subsequent relapses modelled following retreatment. The results of this scenario are associated with substantial uncertainty. Of note, the uptake rate and response rate associated with teprotumumab retreatment as reported in OPTIC-X were in patients who initially responded to teprotumumab; thus, these estimates have uncertain applicability to the modelled retreated population which reflect a mix of responders and non-responders. These assumptions may overestimate the response to retreatment if initial responders are more likely to respond and underestimate the cost of retreatment if there is substantial use in patients who did not respond initially to treatment. Furthermore, the benefit of teprotumumab retreatment may be overestimated due to the assumption of no further relapses. The impact on the ICER due to retreatment has therefore likely been underestimated.

[48] 9/34 (26.5%) proptosis responders following teprotumumab who relapsed and were retreated

[49] Of the 10 proptosis responders who relapsed and were eligible for OPTIC-X, 9 received retreatment as part of the extension study, of whom 5 responded.

Table 19: Key univariate analyses

	Incremental costs	Incremental QALYs	ICER	%
Base case	**$** [redacted]	**1.286**	**$** [redacted] 1	**–**
Include TEP retreatment (efficacy and cost) (base case: not included), see paragraph 6.87.	$ [redacted]	1.325	$ [redacted] 2	[redacted] %
Discount rate, base case: 5%				
• 0%	$ [redacted]	2.542	$ [redacted] 3	– [redacted] %
• 3.5%	$ [redacted]	1.529	$ [redacted] 1	– [redacted] %
Time horizon, base case: 47 years (lifetime)				
• 5 years	$ [redacted]	0.404	$ [redacted] 4	[redacted] %
• 10 years **[#3]**	$ [redacted]	0.681	$ [redacted] 5	[redacted] %
• 15 years	$ [redacted]	0.876	$ [redacted] 6	[redacted] %
TEP source data, OPTIC (base case: pooled TEP trial data)	$ [redacted]	1.136	$ [redacted] 2	[redacted] %
IVMP treatment effect for proptosis vs PBO (Douglas et al. 2022). Base case: -0.16 mm				
• Proptosis difference, lower limit: -1.55 mm	$ [redacted]	1.116	$ [redacted] 2	[redacted] %
• Proptosis difference, upper limit: 1.22 mm	$ [redacted]	1.430	$ [redacted] 1	– [redacted] %
IVMP treatment effect vs PBO. Base case: Cycle 1 (Weeks 1-6). No OR applied to PBO data weeks 6–12				
IVMP cycle 1 and 2, diplopia response OR 2.69 to PBO data weeks 1–12 **[#1]**	$ [redacted]	1.182	$ [redacted] 2	[redacted] %
Relapse cycles 5–12 (base case: TEP: 30%, IVMP: 50%)				
• IVMP relapse rates as for TEP (30%) **[#5]**	$ [redacted]	0.901	$ [redacted] 6	[redacted] %
• Use direct long-term TEP data (to week 72)	$ [redacted]	1.490	$ [redacted] 1	– [redacted] %
Rehabilitative surgery rates [a]				
• 43.8% across all states (i.e. highest value)	$ [redacted]	0.954	$ [redacted] 6	[redacted] %
• 5.0% across all states (i.e. lowest value)	$ [redacted]	1.059	$ [redacted] 1	– [redacted] %
• 0% across all states	$ [redacted]	1.513	$ [redacted] 1	– [redacted] %
SPND and SPID surgery rates (base case: 5%)				
• 20%	$ [redacted]	1.159	$ [redacted] 2	[redacted] %
• 25%	$ [redacted]	1.117	$ [redacted] 2	[redacted] %
Surgery utility (base case: Surgery, 0.30; Post-surgery, 0.43)				
• Post-surgery, 0.60 (as for SPND)	$ [redacted]	1.048	$ [redacted] 2	[redacted] %
• Surgery, 0.38; Post surgery: 0.50 [b] **[#4]**	$ [redacted]	1.153	$ [redacted] 2	[redacted] %
TED symptom health state utility				
• SPND, 0.54 (base case: 0.60)	$ [redacted]	1.013	$ [redacted] 6	[redacted] %
• SPND, 0.67 (base case: 0.60)	$ [redacted]	1.604	$ [redacted] 1	– [redacted] %
• LPID, 0.36 (base case: 0.43)	$ [redacted]	1.494	$ [redacted] 1	– [redacted] %
• LPID, 0.49 (base case: 0.43)	$ [redacted]	1.149	$ [redacted] 2	[redacted] %
• LPCD, 0.24 (base case: 0.30)	$ [redacted]	1.445	$ [redacted] 1	– [redacted] %
• LPCD, 0.36 (base case: 0.30)	$ [redacted]	1.135	$ [redacted] 2	[redacted] %
• Same utility for SPID, LPID, LPND states (median 0.46)	$ [redacted]	1.160	$ [redacted] 2	[redacted] %
TEP compliance, 100% (base case: 91.57%) [#2]	$ [redacted]	1.286	$ [redacted] 2	[redacted] %
Multivariate analysis				
#1 and #2	$ [redacted]	1.182	$ [redacted] 2	[redacted] %
#1, #2 and #3	$ [redacted]	0.624	$ [redacted] 4	[redacted] %
#1, #2, #3 and #4	$ [redacted]	0.573	$ [redacted] 4	[redacted] %
#1, #2, #3, #4 and #5	$ [redacted]	0.385	$ [redacted] 7	[redacted] %

Source: Adapted from Table 3–48, p219 of the submission.

2L = second-line; ICER = incremental cost-effectiveness ratio; IVMP = intravenous methylprednisolone; LPCD = large proptosis with constant diplopia; LPID = large proptosis with intermittent/inconstant diplopia; LPND = large proptosis with no diplopia; OR = odds ratio; PBO = placebo; QALY = quality-adjusted life year; SPID = small proptosis with intermittent/inconstant diplopia; SPND = small proptosis with no diplopia; TED = thyroid eye disease; TEP = teprotumumab

Note: Analyses in italics text were conducted during the evaluation.

[a] Base case (one-off) surgery rates: SPND: 5.0%; LPND: 38.1%; SPID: 5.0%; LPID: 41.3%; SPCD: 43.8%; LPCD: 43.8%
[b] Alternate approach in the submission's workbook to estimating these utilities, based on the average utility for the LPND, LPID, SPCD and LPCD health states for Surgery; and the average of the SPND, LPND, SPID and LPID health states for Post-surgery.
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000
[2] $75,000 to < $95,000
[3] $35,000 to < $45,000
[4] $155,000 to < $255,000
[5] $135,000 to < $155,000
[6] $95,000 to < $115,000
[7] $255,000 to < $355,000

6.88 The submission did not present multivariate analyses. Multivariate analyses were conducted during the evaluation to correct inappropriate assumptions (i.e. exclusion of double-counted teprotumumab compliance and apply the treatment effect for IVMP over the first two cycles, rather than one cycle) and explore the cumulative effect of plausible changes in key areas of uncertainty in the time horizon, post-surgery utility weights and IVMP relapse rates in cycles 5–12. The ICER was highly sensitive to these cumulative changes, though residual uncertainty remains, given the uncertainty in the treatment effect applied for teprotumumab compared to IVMP, surgery rates by TED symptom health state and health state utility values (in particular SPND and applicability of values derived for active to inactive TED).

Drug cost/patient/course

6.89 The per patient cost of teprotumumab and IVMP ± MMF based on use in clinical evidence, the economic model and in the financial estimates are presented in Table 20. While the use of teprotumumab was similar across the teprotumumab trials and economic and financial estimates, variation in the course cost was observed. In the economic analysis a lower course cost was estimated due to the lower cost per dose applied following adjustment for treatment compliance (91.6%). As described in para 6.81 this adjustment double-counted the impact of teprotumumab discontinuation. Further, across the economic and financial analyses it is not appropriate to assume less than one initial dose.

Table 20: Drug cost per patient for proposed and comparator drugs

	Teprotumumab			IVMP ± MMF		
	Trial dose and duration	**Economic model**	**Financial estimates**	**Trial dose and duration [a]**	**Economic model [b]**	**Financial estimates**
Mean dose	Initial: 2.11 vials [c] Continuing: 3.60 vials [c]	Initial: 2.10 vials [d] Continuing: 3.58 vials [d]	Initial: 2.12 vials [e] Continuing: 3.61 vials [e]	IVMP Weeks 1–6: 500 mg per week Weeks 7–12: 250 mg per week	IVMP Weeks 1–6: 500 mg per week Weeks 7–12: 250 mg per week	IVMP Weeks 1–6: 500 mg per week Weeks 7–12: 250 mg per week MMF: 720 mg/day
Mean no. doses per patient	7.7 (OPTIC)	Initial: 0.97 Continuing: 6.50 Total: 7.5	Initial: 0.92 [f] Continuing: 6.41 [f] Total: 7.3	NR	IVMP Weeks 1–6: 5.58 Weeks 7–12: 5.84	IVMP [g] Weeks 1–6: 2.55 Weeks 7–12: 1.28 Revised [h]: Weeks 1-12: 5.10 MMF: 2.38
Cost per dose	Initial: $[redacted] Continuing: $[redacted]	Initial: $[redacted] [i] Continuing: $[redacted] [i]	Initial: $[redacted] Continuing: $[redacted]	NR	IVMP Weeks 1–6: $44 [j] Weeks 7–12: $39 [j]	IVMP: $46 MMF: $202
Cost per course	$[redacted] [k]	$[redacted]	$[redacted]	NR	$485	IVMP: $176 Revised [h]: $469 MMF: $481

Source: Constructed during the evaluation from Table 12–1, p114 of the OPTIC CSR and the 'Attachment 17 Tepezza Economic model.xlsb' and 'Attachment 19 - Tepezza TED Financial Model.xlsx' files included in the submission.
IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; NR = not reported.
[a] The studies included in the clinical evidence did not include MMF.
[b] The economic model presented three separate comparisons: teprotumumab vs IVMP in 1L; teprotumumab vs IVMP + MMF in 1L; and teprotumumab vs tocilizumab in 2L. The use of IVMP in this table is focused on the economic evaluation of 1L teprotumumab therapy relative to IVMP given the limitations of the evidence presented (see para 6.62).
[c] Based on IPD of patient weight in teprotumumab-treated patients across the pooled analysis.
[d] Based on IPD of patient weight in all patients enrolled in OPTIC.
[e] Based on IPD of patient weight in all patients across the pooled analysis.
[f] Based on a treatment compliance of 91.57% to 1 initial dose and 7continuing doses.
[g] Scripts per treatment were based on a treatment compliance of 85% for both IVMP and MMF and assumed vial sharing for IVMP.
[h] Revised to assume no vial sharing for IVMP.
[i] Cost per teprotumumab dose was adjusted for 91.57% compliance.
[j] Cost per IVMP dose was adjusted for 95% compliance in Weeks 1–6, and 85% compliance in Weeks 7–12.
[k] Assuming 1 initial script and 6.7 continuing scripts.

Estimated PBS usage & financial implications

6.90 The submission was considered by DUSC. The submission utilised an epidemiological approach to estimate the extent of use and financial impact of listing teprotumumab for the treatment of active MS TED. The key inputs utilised in the financial analysis are summarised in Table 21.

Table 21: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comments
Eligible population			
Incidence rate of active MS TED - In males - In females	0.54/100,000 2.67/100,000	Bartalena et al., 2020[50] and Laurberg et al., 2012[51]	Due to limited data on the incidence of active MS TED, the evaluation considered that the incidence rates applied were uncertain.
Incident patients	Yr 1: 449 Yr 2: 455 Yr 3: 462 Yr 4: 468 Yr 5: 473 Yr 6: 479	Estimated incidence rate of active MS TED applied to ABS population projections (2022-2071).	This remains uncertain. See comments above.
Prevalent patients (included only in Year 1)	221	Assumption; 50% of incident patients in 2025 (estimated incidence rate applied to ABS population in 2025).	The financial analysis did not consider retreatment with teprotumumab during the active phase and for treatment of disease reactivation.
% of initiating patients who continue treatment	100%	Assumption	This was reasonable.
Treatment utilisation			
Uptake rate	Yr 1: 85% Yr 2: 87.5% Yr 3: 90% Yr 4: 92.5% Yr 5: 95% Yr 6: 95%	Assumption	Since the submission requested a line-agnostic listing, it was assumed that the extent of use of teprotumumab in the 1L and 2L settings would be captured by these uptake rates. The DUSC considered this to be an overestimate. Uptake may be lower, particularly in the first 1-2 years as experience develops.
Duration of teprotumumab treatment	24 weeks	Draft product information	This was reasonable.
Treatment compliance for teprotumumab	91.57%	TED01RV [10] and OPTIC [52] trials	This was consistent with the economic evaluation. However, in the OPTIC trial, the mean number of doses in the teprotumumab arm was 7.7, resulting in a treatment compliance of 96.25%, which was higher than that applied in the submission's base case. While 88% of patients in the TED01RV trial received all 8 infusions, the mean number of doses remains unknown. The DUSC considered treatment compliance to potentially have been overestimated. The DUSC noted that the estimate was consistent with the clinical trials but that real-

[50] Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. Frontiers in Endocrinology. [Review]. 2020 2020-November-30;11.

[51] Laurberg P, Berman DC, Bülow Pedersen I, Andersen S, Carlé A. Incidence and Clinical Presentation of Moderate to Severe Graves' Orbitopathy in a Danish Population before and after Iodine Fortification of Salt. The Journal of Clinical Endocrinology & Metabolism. 2012;97(7):2325-32.

Data	Value	Source	Comments
			world compliance is generally lower than under ideal trial conditions. The DUSC noted compliance with IVMP was 85%,and considered this would be an appropriate proxy measure.
Duration of IVMP + MMF treatment	12 weeks of IVMP and 24 weeks of MMF treatment	EUGOGO protocol	This differs from the Royal Victorian Ear and Eye hospital guidelines which suggests the addition of MMF to IVMP only for patients who do not respond after 3 infusions. The DUSC considered that the difference with the guidelines will have a small impact on the estimates.
Treatment compliance for IVMP + MMF	85%	Teprotumumab Advisory Board Meeting minutes	This was reasonable.
Costs			
Teprotumumab	$[redacted] per 500 mg vial	Proposed AEMP	This was reasonable.
IVMP	$45.96 per 1 g vial	DPMQs, PBS item numbers 5264C, 2193K	This was reasonable.
MMF	$202.14 per pack (360mg x 120 capsules)		
Patient copayment	PBS: $15.87 RPBS: $4.15	PBS utilisation statistics for items: 5264C, 2193K	This was reasonable.
MBS items	-	Not included.	This was not appropriate given that teprotumumab and IVMP are administered intravenously and for different treatment durations and dosing schedules. Further, if teprotumumab is listed as a line agnostic treatment, there may be offsets associated with a reduction in use of orbital radiotherapy. The DUSC considered that the cost of baseline and regular hearing tests should also be included and also considered that there may be cost offsets associated with a reduction in use of orbital radiotherapy.

Source: Table 4-2, p223 of the submission and the DUSC Advice for teprotumumab
1L = first-line; 2L = second-line; ABS = Australian Bureau of Statistics; AEMP = approved ex-manufacturer price; DPMQs = dispensed price for maximum quantities; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; TED = thyroid eye disease

6.91 The incidence rates of active MS TED were sourced from a study that reported incidence rates of TED in Sweden, Minnesota and Denmark. The incidence rates from the Danish study, which was a prospective registry-based study of 143 newly diagnosed patients between 1992 and 2009 in Denmark, was utilised in the submission as it reported incidence rates of active MS TED in males and females. There is limited data to accurately inform the incidence of active MS TED and thus, the incidence of active MS TED remains largely uncertain. The DUSC agreed with the evaluation and considered that the incidence estimates were uncertain, with the potential to be under or over estimated.

6.92 A prevalent population was included in Year 1 only and was estimated by assuming that 50% of the incidence patients diagnosed in the year before listing would fail IVMP therapy and be eligible for teprotumumab therapy. The approach utilised in the submission did not consider retreatment after not responding to teprotumumab or after relapsing following prior teprotumumab during the active phase and did not consider the use of teprotumumab to treat reactivation of disease. Overall, the evaluation considered that the submission may have underestimated the extent of use and the PBS/RPBS costs of associated with the listing of teprotumumab. The DUSC considered that the estimate for Year 1 was reasonable, however may potentially be an overestimate as patients diagnosed in the year prior of listing will most likely be managed according to current local guidelines (IVMP). The DUSC considered that it was more likely that 25% of patients would receive teprotumumab as 2L based on IVMP non-responder/relapse rates reported in the literature. The DUSC also considered that the prevalence estimates for Years 2 to 6 were likely to be an underestimate as treatment of disease reactivation or re-treatment after non-response to the initial 8 doses, or flare, had not been accounted for.

6.93 The financial analysis assumed that if teprotumumab is listed on the PBS, it would replace IVMP + MMF in 100% of treated patients. Further, the submission assumed that all patients would receive MMF in combination with IVMP. This was not consistent with the proposed clinical algorithm for the intended use of teprotumumab which indicated that some patients would receive IVMP following prior teprotumumab; nor did the submission's assumption align with current clinical guidelines that recommend MMF only for patients that do not respond to IVMP after the first 3 infusions. Thus, the reduction in use of IVMP + MMF due to the listing of teprotumumab has been overestimated. On the other hand, the cost offsets were underestimated as the submission assumed vial sharing for IVMP which was not in line with IVMP product information which specifies that one vial is intended for single-use in a single patient and that any unused product should be discarded. The DUSC agreed with the evaluation that teprotumumab would likely displace and not replace IVMP+MMF and that this will need to be considered in the cost offsets.

6.94 No MBS costs were applied to the financial estimates. This was not appropriate given that teprotumumab and IVMP are administered intravenously and for different treatment durations and dosing schedules. Further, if teprotumumab is listed as a line agnostic treatment, there may be cost offsets associated with a reduction in use of orbital radiotherapy. The DUSC considered that the cost of baseline and regular hearing tests should also be included and also considered that there may be cost offsets associated with a reduction in use of orbital radiotherapy.

6.95 The net financial implications of listing teprotumumab, based on the proposed effective price, are presented in Table 22. The submission did not estimate cost implications to the MBS. This was not reasonable as both teprotumumab, and methylprednisolone are administered intravenously but with different dosing frequency and treatment duration. The associated MBS costs were calculated during

the evaluation using MBS item 105 ($49.75, 80% benefit) in line with previous PBAC advice (para 7.15, ravulizumab PSD, March 2021 PBAC meeting).

Table 22: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of teprotumumab						
Number of patients treated	[redacted] 1	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2	[redacted] 2
Total script numbers	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1	[redacted] 1
Estimated financial implications of teprotumumab						
Total cost to PBS/RPBS less copayments [a]	$[redacted] 3	$[redacted] 4	$[redacted] 5	$[redacted] 5	$[redacted] 5	$[redacted] 5
Estimated financial implications for IVMP and MMF						
IVMP: Cost to the PBS/RPBS less copayments	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6
MMF: Cost to the PBS/RPBS less copayments	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6	$[redacted] 6
Cost to PBS/RPBS less copayments [b] Revised [c]	-$[redacted] 7 -$[redacted] 7	-$[redacted] 7 -$[redacted] 7	-$[redacted] 7 -$[redacted] 7	-$[redacted] 7 -$[redacted] 7	-$[redacted] 7 -$[redacted] 7	-$[redacted] 7 -$[redacted] 7
Net financial implications						
Net cost to PBS/RPBS Revised	$[redacted] 3 $[redacted] 3	$[redacted] 4 $[redacted] 4	$[redacted] 5 $[redacted] 5	$[redacted] 5 $[redacted] 5	$[redacted] 5 $[redacted] 5	$[redacted] 5 $[redacted] 5
Net cost to MBS [d]	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7	-$[redacted] 7
Net cost to PBS/RPBS/MBS	**$**[redacted] 3	**$**[redacted] 4	**$**[redacted] 5	**$**[redacted] 5	**$**[redacted] 5	**$**[redacted] 5

Source: Tabulated during the evaluation, from the "Attachment 19 – Tepezza TED Financial Model" workbook provided in the submission.
IVMP = intravenous methylprednisolone; MBS = Medicare benefits schedule; MMF = mycophenolate mofetil; PBS = Pharmaceutical benefits scheme; RPBS = Repatriation pharmaceutical benefits scheme.
[a] Based on weighted dispensed prices of $[redacted] and $[redacted] per initial and continuing dose, respectively.
[b] Assumes vial sharing for IVMP, DPMQs of $45.96 and $202.145 for IVMP and MMF, respectively.
[c] Assumes no vial sharing for IVMP
[d] Estimated using MBS item 105, $49.75 (80% benefit).
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] < 500
[3] $60 million to < $70 million
[4] $40 million to < $50 million
[5] $50 million to < $60 million
[6] $0 to < $10 million
[7] net cost saving

6.96 The DUSC considered the estimates presented in the submission to be overestimated. The main issues identified by DUSC were that:

- There was considerable uncertainty in the incidence rates and that this had a significant impact on the overall utilisation estimates.
- The treatment uptake rates were likely overestimated in the first two years of listing, leading to an overestimate of the financial impact of listing teprotumumab overall. The DUSC suggested an uptake rate by year of: 2026: 60%, 2027: 80%; 2028: 85.0%; 2029: 90.0%, 2030: 95.0%; 2031: 95.0% (capped at 95%).
- The exclusion of retreatment from the financial models, which is not excluded by the current restriction, led to an underestimate in the cost.

6.97 The DUSC advised that minor changes to the methods used to derive the utilisation and financial estimates and structure of the estimates model should be considered:

- Epidemiology of the disease is not well established, sensitivity analysis using a wider range of incident values may be appropriate.
- Minor changes to the treated population, including possible retreatment after non-response, relapse or reactivation where impact on uptake can be estimated with some certainty.
- Changes to some data inputs and assumptions are required including uptake, incidence, and compliance rates but would be supported by additional sensitivity analyses with a range greater than +/- 10% to explore the extent of uncertainty.

Quality Use of Medicines

6.98 The submission noted that routine pharmacovigilance measures are in place to ensure that safe and quality use of teprotumumab in Australia. The submission stated that the sponsor will work collaboratively with healthcare professionals involved in the care for patients with TED to develop materials such as brochures, educational programs and accredited education services which will be distributed and share via multiple platforms. The materials would be targeted to healthcare professionals such as ophthalmologists, endocrinologists, nurses, rheumatologists and oculoplastic surgeons.

6.99 The submission also noted that a post-marketing trial, with 99 patients enrolled, is currently being undertaken in the USA and 5 European countries to assess the safety of teprotumumab with regards to hearing impairment and to assess the tolerability of different treatment durations of teprotumumab (4, 8 and 16 infusions).

6.100 The DUSC noted that patients will have to first visit a referral centre for initial assessment before being treated locally. The DUSC considered that this may cause access issues for rural and remote communities. The DUSC also noted that access to infusion services may be more limited in rural and remote Aboriginal communities.

6.101 The DUSC noted that while hearing loss was not a major issue in the clinical trials, the draft product information included a warning for hearing loss and that appropriate assessments need to be undertaken prior to commencing therapy. The DUSC considered that due to the unknown mechanism of action of the hearing loss and higher rates in real world studies, that as part of the restriction it would be appropriate to include that audiology review and surveillance should be undertaken before and during treatment with teprotumumab. The pre-PBAC Response acknowledged that hearing impairment was an important risk associated with teprotumumab and agreed with the proposed amendment to the restriction.

Financial Management – Risk Sharing Arrangements

6.102 The submission stated that the sponsor would be willing to enter into a risk sharing arrangement (RSA) following a positive recommendation from the PBAC.

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

7 PBAC Outcome

7.1 The PBAC did not recommend teprotumumab for the treatment of active, moderate-to-severe (MS) thyroid eye disease (TED). The PBAC considered there was a high clinical need in the requested patient population, and the evidence presented demonstrated that teprotumumab was more effective in reducing proptosis and diplopia compared to the current standard of care (SoC), which may lead to a reduced utilisation of eye surgery. However, the PBAC considered that due to the limited data available, the complexity of the economic model led to a high degree of uncertainty. The PBAC considered that revision to model inputs and a price reduction would be required to address residual uncertainty and achieve a cost-effective listing, together with a risk sharing arrangement.

7.2 The primary reason for this outcome was due to the economic evaluation presented.

7.3 The PBAC recognised the high clinical need for effective treatments for active MS TED. The PBAC noted that TED follows a biphasic disease course, with an initial active phase lasting 1 to 3 years characterised by progressive inflammation and tissue remodelling. An inactive phase follows, where inflammation subsides but residual effects like proptosis and diplopia may persist due to permanent tissue change. The PBAC noted that early intervention in the active phase is important to mitigate the severity of these symptoms and optimise both functional and structural outcomes.

7.4 The PBAC noted the sponsor hearing and the Consumer comments from organisations, health care professionals and individuals emphasising the high clinical need for effective treatment options for patients with active MS TED. The PBAC noted that comments highlighted that current therapies, such as intravenous corticosteroids, had minimal impact on the severity of disease, as these therapies primarily manage symptoms or reduce inflammation non-specifically and do not target the underlying disease. The PBAC also noted comments emphasised the high burden of disease and suffering associated with TED. The comments described how disfiguring and vision impairing symptoms often led to social withdrawal, depression, and a significantly reduced ability to perform essential everyday activities.

7.5 The PBAC noted the following points regarding the restriction for teprotumumab:

- The proposed clinical activity score (CAS) threshold of ≥ 3 was likely reasonable (paragraph 3.3), given that this threshold usually indicates active TED[52] and the inclusion of a separate clinical criterion restricting treatment to patients with moderate to severe TED (as reported in the 2021 European Group on Graves'

[52] Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. Eur Thyroid J. 2022 Dec 1;11(6)

Orbitopathy [EUGOGO] guidelines[53]).

- Individuals with MS TED but without a diagnosis of Graves' disease (GD) would likely still benefit from treatment with teprotumumab and therefore the exclusion of a requirement for a diagnosis was likely appropriate (paragraph 3.4).
- The PBAC considered that treatment experienced patients who meet the activity (CAS of ≥ 3) and severity criteria (EUGOGO guidelines) in the proposed restriction would likely still benefit from treatment with teprotumumab and therefore considered a line-agnostic listing was likely appropriate.
- The PBAC agreed with the ESC that retreatment with teprotumumab would be appropriate for subsequent episodes of active MS TED, except in cases where there was a poor response to prior treatment.
- The PBAC considered that it would be appropriate to include a stopping rule based on adverse events, efficacy and pregnancy.
- The PBAC agreed with the DUSC that as part of the restriction it would be appropriate to include a requirement for audiology review and surveillance before and during treatment (paragraph 6.101).
- The PBAC considered that treatment should be restricted to adults 18 years of age or older due to the mechanism of action and effects on growth and development.
- The PBAC considered that an Authority Required (telephone/online) immediate assessment (no human operator) would be suitable for the initial restriction.
- The PBAC considered that continuing scripts should be prescribed by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease to improve access and logistics for patients, particularly in rural and remote patients.

7.6 The submission nominated SoC as the comparator consisting of intravenous methylprednisolone (IVMP) with or without mycophenolate mofetil (MMF) in the first-line (1L) setting and tocilizumab in the second-line (2L) setting. The PBAC considered that this was appropriate, however noted that tocilizumab does not currently have registration by the TGA or PBS for this indication and considered that rituximab was also a relevant comparator in the 2L setting.

7.7 The PBAC noted that the submission was based on two head-to-head trials comparing teprotumumab to placebo, in addition to background medication for TED. TEDRV01 (n=88) enrolled patients with Graves' disease associated with active TED. OPTIC (n=83) enrolled patients with Graves' disease associated with active MS TED. Additionally,

[53] Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. European Journal of Endocrinology. 2021;185(4):G43-G67

the OPTIC-X trial (n=51) enrolled patients who completed the 24-week double-masked treatment period of the OPTIC trial who were either proptosis non-responders at week 24 or had relapsed during the OPTIC follow-up period.

7.8 The PBAC noted that the TED01RV and OPTIC trials reported significant reductions in both proptosis and diplopia and significantly improved quality of life scores (Graves' ophthalmopathy quality of life [GO-QOL]) for patients treated with teprotumumab over placebo. Based on the pooled analysis of these studies[54], at Week 24, the mean change in proptosis from baseline at Week 24 was -3.14 mm in the teprotumumab group versus -0.37 mm in the placebo group (difference -2.77 mm, 95% CI: -3.23, -2.31). At Week 24, 70% of patients in the teprotumumab group versus 31% in the placebo group showed diplopia improvement by one grade or more (treatment difference 39%, 95% CI: 23%, 55%). The PBAC also noted that the OPTIC-X extension study demonstrated that patients who received placebo in the OPTIC trial and then received teprotumumab achieved a similar response to treatment to the initial teprotumumab group and achieved sustained responses up to Week 48.

7.9 The PBAC noted that the submission presented an unanchored matching adjusted indirect comparison (MAIC) of teprotumumab versus IVMP in the 1L setting. The PBAC noted the results from the MAIC indicated that teprotumumab was associated with a statistically significantly greater change from baseline in proptosis (mean difference [MD], -2.31 mm, 95% CI: -3.45, -1.17 mm) and a greater odds of diplopia response (odds ratio [OR], 2.32, 95% CI: 1.07, 5.03) compared to IVMP. However, the PBAC noted that these results were highly uncertain due to numerous transitivity issues (paragraphs 6.28) and noted advice from the ESC that the MAIC was unreliable and did not adequately account for the complexity of treatment for TED (paragraph 6.53).

7.10 The PBAC noted that the submission presented a Bucher ITC between teprotumumab and tocilizumab for the 2L treatment of TED using placebo as a common comparator. The PBAC noted that based on the ITC, the relative risk (RR) of proptosis response was 2.6 (95% CI: 1.25, 5.41) in favour of teprotumumab, and patients treated with tocilizumab were twice as likely to be non-responders compared with patients treated with teprotumumab (0.47, 95% CI: 0.34, 0.66) in terms of diplopia. However, the PBAC noted that the Bucher ITC was uncertain due to differences in the studies included leading to substantial bias and noted advice from the ESC that the results were unreliable (paragraph 6.56).

7.11 Overall, the PBAC considered that while there was significant uncertainty related to the ITCs presented, the totality of the available evidence suggests that the claim of superior efficacy of teprotumumab versus IVMP in the 1L setting and versus tocilizumab in the 2L setting was likely reasonable. This conclusion is supported by

[54] Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. *Lancet Diabetes Endocrinol*. 2021 Jun;9(6):360-72.

consistent trends across multiple clinically relevant endpoints, including proptosis and diplopia response, and across multiple analyses, where teprotumumab demonstrated a statistically increased likelihood of response compared with SoC therapies. However, the PBAC considered that the magnitude of treatment effect of teprotumumab versus SoC is uncertain due to the substantial transitivity violations across the comparisons.

7.12 The PBAC noted that the submission did not present a formal comparison of safety for teprotumumab versus IVMP or tocilizumab. The PBAC further noted that while there were significant safety concerns associated with teprotumumab, including permanent hearing impairment, as well as other common adverse events, that IVMP with or without MMF and tocilizumab were also associated with significant safety risks. Overall, the PBAC considered that the claim of non-inferior comparative safety of teprotumumab versus the current SoC therapies to be uncertain, but likely reasonable.

7.13 The PBAC noted that the submission presented a cost-utility analysis for the economic evaluation. The PBAC noted that the comparison of teprotumumab versus IVMP in the 1L setting was based on the unanchored MAIC that compared pooled and adjusted data from the key teprotumumab (TED01RV and OPTIC) and IVMP studies. The PBAC noted that the base case incremental cost-effectiveness ratio (ICER) for the economic model was associated with a high level of uncertainty ($55,000 to < $75,000/quality adjusted life year [QALY] gained). The PBAC agreed with the ESC that the health states included in the economic model likely reflected clinically meaningful differences for MS TED patients, however its complexity led to a high degree of uncertainty due to insufficient data to reliably inform a model with numerous transition probabilities with projected long-term outcomes over a lifetime time horizon.

7.14 The PBAC noted that the economic model also included several optimistic and inappropriate parametric assumptions, which favoured teprotumumab. The PBAC noted that the economic model had likely double-counted the impact of teprotumumab discontinuation (paragraph 6.81) and the IVMP treatment effect for diplopia had been applied to cycle 1 only (i.e. to week 6), which was not consistent with the data from the MAIC which reported the odds of improved response to 12 weeks (paragraph 6.71). The PBAC agreed with the evaluation that these assumptions were not appropriate and noted that correction to these led to a [redacted]% increase in the ICER (multivariate analysis #1 + #2, Table 19).

7.15 The PBAC also noted that the submission adopted a lifetime time horizon, which was substantially longer than the duration of evidence available for teprotumumab (up to 72 weeks). The PBAC noted that the magnitude of the teprotumumab treatment effect versus SoC was uncertain (paragraph 7.11) and the extent to which teprotumumab reduced the need for surgical intervention and the comparative long-term functional and anatomical outcomes versus SoC remained unclear. For these reasons, the PBAC considered that a 20-year time horizon would be more appropriate.

7.16 The PBAC noted that there was also a high degree of uncertainty related to the health state utility values applied to the economic model (paragraphs 6.77−6.78). The PBAC agreed with the ESC that the values were very low, ranging between 0.30–0.60 for the most to least severe health states, and did not accurately reflect the quality of life of individuals with MS TED during the active and inactive phases of disease, nor long-term, during and after surgery and over a lifetime. The PBAC considered that alternative utility-weights would be required to ensure the overall validity of the economic model, particularly over a lifetime time horizon.

7.17 Notwithstanding the remaining uncertainties with the economic model, but noting the high unmet clinical need for individuals with MS TED, the PBAC foreshadowed that use of a respecified model would be appropriate in a resubmission with (i) the removal of double counting of teprotumumab discontinuation (paragraph 7.14); (ii) the IVMP treatment effect applied up to Week 12 in the model (paragraph 7.14); (iii) a 20-year time horizon (paragraph 7.15); (iv) alternate utility-weights applied to the model (paragraph 7.16); and (v) a price reduction reflective of an ICER of <$75,000 per QALY gained.

7.18 The PBAC noted the DUSC advice that the modelled utilisation was likely overestimated, primarily due to the assumption that that treatment uptake would be high in the first two years of listing (Year 1: 85%; Year 2: 87.5%). The PBAC also noted the exclusion of retreatment, however considered the impact was likely relatively small over the 6 year forward estimates. Overall, the PBAC considered that the utilisation estimates would be reasonable if the uptake was reduced. The PBAC considered that the DUSC suggested treatment uptake would be appropriate (Y1: 60%, Y2: 80%; Y3: 85.0%; Y4: 90.0%, Y5: 95.0%; Y6: 95.0%) (DUSC ADV, March 2025). The PBAC noted that the financial estimates should be updated to include relevant MBS costs associated with administration, regular hearing tests, and the potential for a reduction in the use of orbital radiotherapy.

7.19 The PBAC considered that a Risk Sharing Arrangement (RSA), with a rebate of 100% for use above the expenditure caps would be required to mitigate risk of use in chronic (inactive) and less severe disease.

7.20 The PBAC considered the outstanding issues could be resolved in a simple resubmission for teprotumumab. The PBAC also considered teprotumumab addresses a high and unmet clinical need and was expected to provide a significant and clinically relevant improvement in efficacy over SoC. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- A revised restriction that incorporates the changes outlined in paragraph 7.5;
- Revision to inputs in the economic model as outlined in paragraph 7.17.
- Revision of the financial estimates as outlined in paragraph 7.18 and recalculation

of the financial implications using the revised teprotumumab price; and

- An RSA as outlined in paragraph 7.19.

7.21 The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

7.22 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

Amgen is committed to work with the PBAC and Department of Health to facilitate timely access to teprotumumab through the early resolution pathway. Amgen would like to thank all of the healthcare professionals, professional societies, patient organisations and consumers for their support of the submission.

Addendum to the March 2025 Public Summary Document:

7.04 TEPROTUMUMAB, Powder for I.V. infusion 500 mg, Tepezza®, AMGEN AUSTRALIA PTY LTD.

10 Background

10.1 The early resolution resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required listing for teprotumumab for the treatment of active, moderate-to-severe (MS) thyroid eye disease (TED).

10.2 Teprotumumab was considered by the PBAC and not recommended for PBS listing at the March 2025 meeting. At the meeting, the PBAC accepted that there was a high clinical need in the requested patient population, and the evidence presented demonstrated that teprotumumab was more effective in reducing proptosis and diplopia compared to the current standard of care (SoC), which may lead to a reduced utilisation of eye surgery. However, the PBAC considered that due to the limited data available, the complexity of the economic model led to a high degree of uncertainty. The PBAC considered that revision to model inputs and a price reduction would be required to address residual uncertainty and achieve a cost-effective listing, together with a risk sharing arrangement (RSA).

10.3 The PBAC considered that the outstanding issues could be addressed using the early resolution pathway if the matters were addressed as outlined in Table 23. A summary of the resubmission's approach to these matters is also provided in Table 23.

Table 23: Summary of changes made in the resubmission

PBAC minutes recommended change March 2025	Early resolution resubmission change May 2025	Addressed?
Requested listing		
The proposed CAS threshold of ≥ 3 was likely reasonable.	The resubmission retained a CAS threshold of ≥ 3.	Yes
The exclusion of a GD diagnosis was likely appropriate.	The resubmission continued to exclude a requirement for a GD diagnosis.	Yes
A line-agnostic listing was likely appropriate.	The resubmission maintained a line-agnostic listing.	Yes
Retreatment with teprotumumab would be appropriate for subsequent episodes of active MS TED, except in cases where there was a poor response to prior treatment.	The resubmission proposed the following clinical criterion for the initial treatment phase to limit retreatment to prior responders: *'Patient must not have previously failed PBS-subsidised therapy with this drug for this condition'*	Partially
It would be appropriate to include a stopping rule based on adverse events, efficacy and pregnancy.	The resubmission proposed cautions, rather than a stopping rule related to pregnancy and audiology monitoring. A stopping rule for efficacy was not proposed.	Partially
It would be appropriate to include a requirement for audiology review with surveillance before and during treatment.	The resubmission proposed the following caution related to audiology monitoring: *Assess patients' hearing before, and routinely during and after treatment, including use of audiograms where clinically warranted.*	Partially
Treatment should be restricted to adults 18 years of age or older due to the mechanism of action and effects on growth and development.	The resubmission included a population criterion restricting treatment to individuals at least 18 years of age.	Yes
An Authority Required (telephone/online) immediate assessment (no human operator) would be suitable for the initial restriction.	The resubmission requested an Authority Required (telephone/online) listing for the initial treatment phase.	Yes
Continuing scripts should be prescribed by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease to improve access and logistics for patients, particularly in rural and remote patients.	The resubmission included a treatment criterion for the continuing treatment phase which requires prescribing of teprotumumab to be by a specialist physician experienced in the management of thyroid eye disease or by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease.	Yes
Economic model		
Removal of double counting of teprotumumab discontinuation.	The resubmission presented a revised base case with teprotumumab compliance set to 100%, removing double counting of discontinuation.	Yes

PBAC minutes recommended change March 2025	Early resolution resubmission change May 2025	Addressed?
The IVMP treatment effect for diplopia should be applied up to Week 12 in the model.	The resubmission calculated a per-week odds ratio (1.64), which was applied to the IVMP arm of the model up to Week 12 in the revised base case.	Yes
A 20-year time horizon.	In the revised base case, the time horizon was set to 20 years.	Yes
Utility weights should be revised to more accurately reflect the QoL of individuals with MS TED during the active and inactive phases of disease, and long-term, during and after surgery.	Alternate utility weights were applied to the revised base case and sought to more accurately reflect the QoL of individuals with MS TED.	Yes
A price reduction reflective of an ICER of <$75,000 per QALY gained.	The resubmission proposed a price reduction of [redacted]%. The effective ex-manufacturer's price was reduced from $[redacted] to $[redacted] per vial. The revised ICER was $[redacted] [1] per QALY gained.	Yes
Financial estimates		
Revision to uptake rates, as per DUSC advice (Y1: [redacted]%, Y2: [redacted]%; Y3: [redacted]%; Y4: [redacted]%, Y5: [redacted]%; Y6: [redacted]%)	The resubmission applied the DUSC suggested uptake rates.	Yes
Inclusion of MBS costs for administration, regular hearing tests, and the potential for a reduction in the use of orbital radiotherapy.	The resubmission included MBS costs.	Yes
Risk sharing arrangements		
Inclusion of an RSA with a rebate of [redacted]% for use above the expenditure caps to mitigate risk of use in chronic (inactive) and less severe disease.	The resubmission proposed a stepped RSA, which included a step that accounted for possible retreatment and a [redacted]% rebate.	Partially

Abbreviations: CAS = clinical activity score, GD = Graves' disease; IVMP = intravenous methylprednisolone; MS TED = moderate-to-severe thyroid eye disease; ICER = incremental cost effectiveness ratio; LY = life year, QALY = Quality adjusted life year, QoL = quality of life; RSA = Risk Sharing Arrangement. DUSC = Drug Utilisation Sub-Committee, MBS = Medical benefits schedule, m = million.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*

11 Requested listing

11.1 At the March 2025 PBAC meeting, the PBAC advised that the proposed restriction required revision (paragraph 7.5). Aligned with this advice, the resubmission:

- retained a clinical activity score (CAS) threshold of ≥3;
- continued to exclude the requirement for a Graves' disease (GD) diagnosis;
- maintained a line-agnostic listing;

- included a population criterion restricting treatment to individuals at least 18 years of age;
- requested an Authority Required (telephone/online) listing for the initial treatment phase; and
- included a treatment criterion for the continuing treatment phase which requires prescribing of teprotumumab to be by a specialist physician experienced in the management of thyroid eye disease or by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease.

11.2 The PBAC also considered that retreatment with teprotumumab would be appropriate for subsequent episodes of active MS TED, except in cases where there was a poor response to prior treatment (paragraph 7.5). In response, the resubmission proposed a clinical criterion for the initial treatment phase limiting retreatment to prior responders. This was aligned with previous PBAC advice. However, given there is no defined treatment duration in the restriction, retreatment could be mistakenly initiated through the proposed continuing treatment phase and bypass the activity (CAS of ≥ 3) and severity criteria (2021 European Group on Graves' Orbitopathy [EUGOGO] guidelines) for retreatment. The Secretariat considered that it may be appropriate for the restriction to state that a treatment course is 8 doses in total, and reinitiating patients should again be prescribed the initial 10 mg/kg dose through the initial treatment phase.

11.3 The PBAC previously considered that it would be appropriate to include a stopping rule based on adverse events, efficacy, and pregnancy (paragraph 7.5). The resubmission proposed cautions, rather than a stopping rule related to pregnancy and audiology monitoring. Cautions are administrative advice and not legally binding. Furthermore, based on clinician feedback, a stopping rule for efficacy was not proposed. The submission stated that a specific time point during the eight infusions (24 weeks) to determine response to treatment was not evident in the results of the teprotumumab clinical trials. Furthermore, a 'responder' was defined in the OPTIC clinical trial as a patient who had a decrease of ≥2mm from baseline in proptosis and ≥2 point in overall reduction in CAS at Week 24 (i.e. after all eight infusions had been administered). Moreover, on review of the clinical evidence, the mean change in proptosis after 24 weeks (-2.82 [0.191]mm) did not result in a statistically significant decrease until the end of the follow-up period at week 72 (-3.62 [1.387] mm) and increases between week 24 and 28 (-3.51 [1.738mm]). The submission stated that this indicated that response to teprotumumab continues to increase after treatment has been completed, and therefore a pre-defined point to assess response may be clinically inappropriate.

11.4 Due to safety concerns related to hearing impairment, the PBAC previously considered that as part of the restriction it would be appropriate to include a requirement for audiology review and surveillance before and during treatment (paragraph 7.5). In response, the resubmission proposed a caution stating that a patient's hearing should

be assessed before, and routinely during and after treatment, including use of audiograms where clinically warranted. Cautions are administrative advice and not legally binding.

For more detail on PBAC's view, see section 13 PBAC outcome.

12 Consideration of the evidence

Economic analysis

12.1 As an early resolution resubmission, the updated economic evaluation has not been independently evaluated.

12.2 At the March 2025 PBAC meeting, the PBAC considered that revision to inputs in the economic model and a price reduction would be required to address residual uncertainty and achieve a cost-effective listing (paragraph 7.17). Aligned with this advice, the resubmission presented a re-specified base case which:

- removed the double counting of teprotumumab discontinuation by increasing teprotumumab compliance from 91.57% to 100%;
- corrected the length of the intravenous methylprednisolone (IVMP) treatment effect by applying a per-week odds ratio (1.64) to the IVMP arm of the model up to Week 12;
- reduced the time horizon from 47 years (lifetime) to 20 years;
- applied alternate utility-weights; and
- proposed a price reduction of [redacted]%.

12.3 The PBAC previously noted that the IVMP treatment effect for diplopia had been applied to cycle 1 only (i.e. to week 6), which was not consistent with the data from the unanchored matching adjusted indirect comparison (MAIC) which reported the odds of improved response to 12 weeks (paragraphs 6.71, 7.14). The resubmission noted that the previous evaluation, in attempt to correct for the error in a sensitivity analysis, applied the diplopia response odds ratio (OR) to 2.69 to weeks 1–12 (Table 17 and Table 19), which likely over inflated the efficacy of IVMP in cycles 1 and 2. The resubmission noted that with two 6-week cycles for IVMP treatment, a per-cycle OR was required to account for the cumulative effect over two cycles which equalled the original 12-week OR. The calculation was for 6 weeks = sqrt(OR_12 week) = sqrt(2.69) ≈ 1.64. The resubmission's approach for estimating the IVMP treatment effect resulted in an increase in the incremental cost-effectiveness ratio (ICER) from $55,000 to < $75,000 to $75,000 to < $95,000, when applied to the March 2025 economic model.

12.4 The PBAC previously noted that there was also a high degree of uncertainty related to the health state utility values applied to the economic model (paragraphs 6.77–6.78, 7.16). The PBAC considered that alternative utility-weights would be required to

ensure the overall validity of the economic model. The resubmission sought to address these concerns through an 'anchor-based approach', whereby utility estimates were recalibrated relative to a normative baseline. The health state with the highest health-related quality of life (HRQoL) pre-surgery, defined as small proptosis with no diplopia, was assumed to represent a near-normal level of functioning and quality of life (QoL). This utility was increased by 0.25 to 0.85 and is close in value to the utility estimated as the population norm in Australia (0.86; Redwood et. al. 2023[55]) and served as the 'anchor state' for estimating the utility of all other health states. Utility values for the remaining pre-surgery health states were calculated by applying the decrements between health states as reported in Smith et al. 2023[56]. The revised pre-surgery values are presented in Table 28.

12.5 The resubmission also revised the utility values for health states related to surgery and post-surgery. A decrement in utility was applied on transition to the surgical phase that was relative and proportionate to the health state the patient was in prior to surgery. Secondly, an improvement in utility was then applied to reflect a clinical improvement from surgery, again relative and proportionate to the starting TED health state. These movements in and out of surgery across each of the six health states aimed to reflect the individual surgical journeys expected for patients living with TED. This was not possible in the original model which used a single health state value for the surgical phase and post-surgical phase, independent of treatment arm.

12.6 To reflect reduced utility in the surgical phase, a decrement of 0.05 was applied to the small proptosis health states and a decrement of 0.1 was applied to the large proptosis health states (Table 24). The resubmission stated that a larger decrement was applied for large versus small proptosis due to patients with large proptosis requiring more invasive bony wall rather than fat-only decompression surgeries, which are more complex and consequently impactful on quality of life. However, no decrements were applied to surgery for large proptosis, constant diplopia and a smaller decrement (0.04) was applied for surgery for small proptosis, constant diplopia. This was because the resubmission assumed a 'floor' utility of 0.55 across all health states. A comparison of the utility values during the surgery phase from the March 2025 model versus the re-specified model in the resubmission is provided in Table 25.

[55] Redwood, L., Currow, D., Kochovska, S. & Thomas, S. J. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. Qual Life Res 33, 721-733 (2024). https://doi.org/10.1007/s11136-023-03558-z

[56] Smith, T. J. et al. Utility Assessment of Moderate to Severe Thyroid Eye Disease Health States. JAMA Ophthalmol 141, 159-166 (2023). https://doi.org/10.1001/jamaophthalmol.2022.3225

Table 24: Comparison of the decrements due to surgery from the March 2025 versus the re-specified model in the resubmission

Health state	Decrement due to surgery (March 2025 model)	Decrement due to surgery (Resubmission model)
Small Proptosis, No Diplopia	0.3	0.05
Large Proptosis, No Diplopia	0.16	0.1
Small Proptosis, Intermittent/Inconstant Diplopia	0.22	0.05
Large Proptosis, Intermittent/Inconstant Diplopia	0.13	0.1
Small Proptosis, Constant Diplopia	0.04	0.04
Large Proptosis, Constant Diplopia	0	0

Source: Resubmission, Table 9, p8

Table 25: Comparison of utility during the surgery phase in the March 2025 versus the re-specified model in the resubmission

Health state	Utility during surgery (March 2025 model)	Utility during surgery (Resubmission model)
Small Proptosis, No Diplopia	0.55	0.80
Large Proptosis, No Diplopia	0.55	0.61
Small Proptosis, Intermittent/Inconstant Diplopia	0.55	0.72
Large Proptosis, Intermittent/Inconstant Diplopia	0.55	0.58
Small Proptosis, Constant Diplopia	0.55	0.55
Large Proptosis, Constant Diplopia	0.55	0.55

Source: Resubmission, Table 10, p8

12.7 To reflect an improvement in quality of life following rehabilitative surgery, the resubmission also revised the post-surgical utility weights (Table 26). Similar to the approach taken in the surgical phase, the utility gains following surgery were proportionate to the severity of the starting health state. The health states associated with the most severe disease were assumed to gain the most utility from surgery (0.22), while the health states with less severe disease gained the least (0.05 for small proptosis, no diplopia and 0.13 for small proptosis, intermittent/inconstant diplopia). The two intermediate health states defined by large proptosis differed slightly in the utility gain achieved from surgery with a greater improvement modelled for intermittent/inconstant diplopia (0.19) versus no diplopia (0.16).

12.8 The revised approach assumed the three health states with the highest quality of life, resulted in a post-surgery utility of 0.85, the same value as the highest TED health state pre-surgery, and the three health states with the lowest quality of life, resulted in a post-utility of 0.77, the same as the second-highest utility pre-surgery. A comparison of the utility values during the post-surgery phase from the March 2025 model versus the re-specified model in the resubmission is provided in Table 27.

Table 26: Comparison of the utility gains post-surgery from the March 2025 versus the re-specified model in the resubmission

Health state	Utility gains post-surgery (March 2025 model)	Utility gains post-surgery (Resubmission model)
Small Proptosis, No Diplopia	0.13	0.05
Large Proptosis, No Diplopia	0.13	0.16
Small Proptosis, Intermittent/Inconstant Diplopia	0.13	0.13
Large Proptosis, Intermittent/Inconstant Diplopia	0.13	0.19
Small Proptosis, Constant Diplopia	0.13	0.22
Large Proptosis, Constant Diplopia	0.13	0.22

Source: Resubmission, Table 11, p9

Table 27: Comparison of utility during post-surgery phase in the March 2025 vs re-specified resubmission model

Health state	Utility during post-surgery phase (March 2025 model)	Utility during post-surgery phase (Resubmission model)
Small Proptosis, No Diplopia	0.68	0.85
Large Proptosis, No Diplopia	0.68	0.85
Small Proptosis, Intermittent/Inconstant Diplopia	0.68	0.85
Large Proptosis, Intermittent/Inconstant Diplopia	0.68	0.77
Small Proptosis, Constant Diplopia	0.68	0.77
Large Proptosis, Constant Diplopia	0.68	0.77

Source: Resubmission, Table 12, p9

12.9 The submission noted that not all patient's achieved a 'full recovery' in utility (assumed as a value of 0.85), which was stated to be a reasonable assumption considering that post-operative diplopia, dry eye, residual disfigurement and depressive symptoms often persist despite rehabilitative surgical intervention for TED.

12.10 The revised utility weights in the resubmission are summarised in Table 28.

Table 28: Revised utility weights in the re-specified resubmission model

Health state	Utility pre-surgery	Utility during surgery phase	Utility post-surgery
Small Proptosis, No Diplopia	0.85	0.80	0.85
Large Proptosis, No Diplopia	0.71	0.61	0.85
Small Proptosis, Intermittent/Inconstant Diplopia	0.77	0.72	0.85
Large Proptosis, Intermittent/Inconstant Diplopia	0.68	0.58	0.77
Small Proptosis, Constant Diplopia	0.59	0.55	0.77
Large Proptosis, Constant Diplopia	0.55	0.55	0.77

Source: Resubmission, Table 8, p7

12.11 Utility estimates for the surgical and post-surgical phases were weighted by the distribution of patients entering surgery from each health state by treatment arm and multiplying these weights by the corresponding health state utility values to generate an average utility for patients requiring surgery in each treatment arm. The calculated weighted utilities assumed that the teprotumumab arm had higher utility values compared to the IVMP arm (Table 29).

Table 29: Weighted utility values in the re-specified resubmission model

	Teprotumumab	IVMP
Surgery	0.62	0.58
Post-surgery	0.82	0.79

Source: Resubmission, Table 13, p10

12.12 The resubmission also proposed a price reduction of [redacted]%. The effective ex-manufacturer's price was reduced from $[redacted] to $[redacted] per vial.

12.13 The revised results of the economic evaluation are presented in Table 30. The ICER was $55,000 to < $75,000 per QALY gained.

Table 30: Results of the re-specified resubmission model compared with the March 2025 model

	Teprotumumab	IVMP	Incremental	ICER
Re-specified model of the resubmission				
Total cost	$[redacted]	$42,852	$[redacted]	-
LYs	12.63	12.63	0.00	-
QALYs	9.74	8.77	0.967	$[redacted] [1]
March 2025 submission				
Total cost	$[redacted]	$46,932	$[redacted]	-
LYs	16.13	16.13	0.00	-
QALYs	8.10	6.82	1.286	$[redacted] [1]

Source: Resubmission, Table 15, p12; March 2025 submission, Table 3−38, p215, Attachment 17 Tepezza Economic model.xlsb
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000

For more detail on PBAC's view, see section 13 PBAC outcome.

Estimated PBS usage & financial implications

12.14 As an early resolution, the estimated utilisation and financial implications have not been independently evaluated.

12.15 Aligned with PBAC advice from the March 2025 meeting (paragraph 7.18), the resubmission:

- reduced the estimated treatment uptake of teprotumumab to Y1: [redacted]%, Y2: [redacted]%; Y3: [redacted]%; Y4: [redacted]%, Y5: [redacted]%; Y6: [redacted]% (DUSC ADV, March 2025); and
- included MBS costs associated with administration, regular hearing tests, and the potential for a reduction in the use of orbital radiotherapy.

12.16 The resubmission assumed patients treated with teprotumumab would utilise the MBS item 14245 for each of the eight infusions required for a course of treatment. Patients treated with IVMP were also assumed to utilise this MBS item for each of the twelve infusions required for a course. A compliance rate of 100% was applied to the teprotumumab infusion utilisation and a compliance rate of 85% was applied to the IVMP infusion utilisation, in line with the compliance used in the economic model. Substitution of IVMP by teprotumumab resulted in an estimated net cost-saving to the MBS per year.

12.17 The resubmission assumed that patients would require a hearing test (MBS item 82306) prior to teprotumumab treatment, during treatment and after treatment (three tests in total). The inclusion of hearing tests for teprotumumab patients resulted in an estimated increase in the MBS budget of between $0 to < $10 million and $0 to < $10 million per year.

12.18 To calculate the cost of orbital radiotherapy, the resubmission assumed that for each patient a planning MBS item 15950 and 10 fractions of MBS item 15956 would be required, based on Bradley et al. 2008[57].

12.19 Based on clinician input, it was assumed for patients that would have been treated with IVMP, 40% would have a partial or minimal response, and therefore require mycophenolate mofetil (MMF). Of patients who have partial/minimal response, 35% would receive orbital radiation. Combining these percentages, the assumption was made that 14% (0.4 × 0.35) of the patient population each year treated with teprotumumab would no longer require orbital radiation. This assumption was applied to the cost of a course of radiotherapy to quantify the potential reduction in the use of radiotherapy with listing of teprotumumab. The PBS listing of teprotumumab was estimated to result in between < 500 and < 500 radiotherapy planning MBS items avoided per year, and between 500 to < 5,000 and 500 to < 5,000 radiotherapy sessions avoided per year. These avoided sessions would translate to an estimated net cost saving per year to the MBS.

12.20 The revised estimated financial implications of listing teprotumumab are presented in Table 31.

[57] Bradley, E. A. et al. Orbital radiation for graves ophthalmopathy: a report by the American Academy of Ophthalmology. Ophthalmology 115, 398-409 (2008).

Table 31: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Resubmission revised estimates						
Estimated extent of use of teprotumumab						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total script numbers	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of teprotumumab						
Cost to PBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]
Cost to RPBS less copayments	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][4]	**$**[redacted][4]
Cost to MBS	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]
Net cost PBS/RPBS/MBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][4]	**$**[redacted][4]
March 2025 submission						
Net cost PBS/RPBS/MBS	**$**[redacted][7]	**$**[redacted][4]	**$**[redacted][8]	**$**[redacted][8]	**$**[redacted][8]	**$**[redacted][8]

Source: Resubmission, Attachment 2 - Tepezza TED Financial Model resub.xlsx; March 2025 submission, Attachment 19 – Tepezza TED Financial Model.xlsx

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$30 million to < $40 million*

[4] *$40 million to < $50 million*

[5] *$0 to < $10 million*

[6] *net cost saving*

[7] *$60 million to < $70 million*

[8] *$50 million to < $60 million*

For more detail on PBAC's view, see section 13 PBAC outcome.

Financial Management – Risk Sharing Arrangements

12.21 At the March 2025 meeting, the PBAC considered that an RSA, with a rebate of [redacted]% for use above the expenditure caps would be required to mitigate risk of use in chronic (inactive) and less severe disease (paragraph 7.19).

12.22 The resubmission noted that the proposed restriction allows patients to be retreated with teprotumumab, however this usage was not included in the financial analysis. Therefore, the resubmission proposed a tiered RSA (Table 32) in which a [redacted]% rebate would apply between tiers 1 and 2 and a [redacted]% rebate would apply above tier 2. The submission stated that the financial estimates for tier 2 was based on the DUSC's consideration that up to 24% of patients may require retreatment. The DUSC advice included a sensitivity analysis with retreatment applied in years 2−6 of listing (March 2025 DUSC advice) based on Ugradar et al 2025[58].

[58] Ugradar S, Parunakian E, Malkhasyan E, Chiou CA, Walsh HL, Tolentino J, Wester ST, Freitag SK, Douglas RS. The Rate of Re-treatment in Patients Treated with Teprotumumab: A Multicenter Study of 119 Patients with 1 Year of Follow-up. Ophthalmology. 2025 Jan;132(1):92-97

Table 32: Proposed risk-sharing arrangement

	Year 1	Year 2	Year 3	Year 4	Year 5
Tier 1	$	$	$	$	$
Tier 2	$	$	$	$	$

Source: Resubmission, Table 30, p20

For more detail on PBAC's view, see section 13 PBAC outcome.

13 PBAC Outcome

13.1 The PBAC recommended the listing of teprotumumab for the treatment of active, moderate-to-severe (MS) thyroid eye disease (TED). The PBAC reaffirmed its previous view that there is a high clinical need in the requested patient population, and that the evidence demonstrated that teprotumumab is more effective in improving proptosis and diplopia compared to current standard of care, which may also lead to a reduced utilisation of eye surgery. The PBAC considered that there remained uncertainty related to the structure and the data informing the economic model. However, the PBAC noted that changes to the economic evaluation and financial estimates had reduced uncertainty and addressed the Committee's concerns. The PBAC considered that teprotumumab would be cost-effective at the price proposed in the resubmission. The PBAC noted that the resubmission proposed a Risk Sharing Arrangement (RSA) and considered that the approach taken was reasonable, however required further revision. Overall, the PBAC considered that the resubmission had addressed the outstanding issues identified at the March 2025 PBAC meeting.

13.2 The PBAC noted that the restriction proposed in the resubmission aligned with a number of changes recommended at the March 2025 meeting. The PBAC noted that:

- the resubmission proposed a clinical criterion for the initial treatment phase limiting retreatment to prior responders. The PBAC considered that this was appropriate, however noted further revision was required so that retreatment was not mistakenly initiated through the proposed continuing treatment phase and bypass the activity (clinical activity score [CAS] of ≥ 3) and severity criteria (2021 European Group on Graves' Orbitopathy [EUGOGO] guidelines) for retreatment.
- the resubmission proposed cautions, rather than a stopping rule related to pregnancy and audiology monitoring. The PBAC considered that this was likely reasonable.
- a stopping rule for efficacy was not proposed. The PBAC considered that this was likely reasonable, noting the justifications made by the resubmission, and agreed that given response to teprotumumab continues to increase over time, a pre-defined point to assess response may not be clinically appropriate. The PBAC also noted that in urgent vision threatening cases, if a patient is not responding to teprotumumab, clinicians were likely to cease treatment and consider surgery.

13.3 The PBAC recalled that at the March 2025 PBAC meeting, it considered that the economic model was associated with a high level of uncertainty. The PBAC reiterated that the complexity of the model led to a high degree of uncertainty due to insufficient data to reliably inform a model with numerous transition probabilities with projected long-term outcomes. The PBAC emphasised that the structure of the economic model remained a significant limitation for the consideration of the cost-effectiveness of teprotumumab. To address the uncertainty in the model, the PBAC noted that the resubmission proposed a re-specified base case with revised inputs. The PBAC noted that the changes to the model aligned with its previous advice (paragraphs 7.14 to 7.17). The PBAC noted that significant revision had been made to the utility weights in the economic model (paragraphs 12.4−12.11). The PBAC considered that while the revised utility weights were subject to some uncertainty, due to values primarily being based on assumptions and not measured outcomes from empirical research, that the revised utility weights appeared to have greater face validity compared to the values applied to the economic model in the March 2025 submission. The PBAC also noted that a price reduction had been proposed which aligned with an incremental cost-effectiveness ratio (ICER) of less than $75,000 per quality adjusted life year (QALY) gained. Overall, the PBAC considered that while uncertainty remained related to the structure and the data informing the economic model, that the changes made had reduced uncertainty, and in the context of a rare disease with a high and unmet clinical need, the ICER of $55,000 to < $75,000 per QALY gained based on the revised model was acceptable.

13.4 The PBAC accepted that the resubmission largely addressed its concerns related to the financial estimates raised at the March 2025 consideration in terms of revising the uptake rate, the inclusion of MBS costs, and a price reduction (paragraph 7.18). The PBAC considered that the revised financial estimates were reasonable.

13.5 The PBAC recalled it had considered that an RSA, with a rebate of [redacted]% for use above the expenditure caps, would be required to mitigate the use in chronic (inactive) and less severe disease (paragraph 7.19) and noted that the resubmission had proposed a 2-tier RSA with the second tier allowing for 24% of patients who may be retreated with teprotumumab (Table 32). The PBAC noted that this percentage was aligned with previous DUSC advice (March 2025 DUSC advice) and Ugradar et al 2025[59]. The PBAC considered that this percentage was reasonable. However, the PBAC considered that there was likely to be a delay between the listing of teprotumumab and the onset of retreatment and therefore considered that the incorporation of retreatment in the RSA should start from the second year of listing. The PBAC therefore considered that a [redacted]% rebate for use above tier 1 should apply to the first year of listing and the resubmission's proposal for a [redacted]% rebate for use above the tier 1 expenditure cap

[59] Ugradar S, Parunakian E, Malkhasyan E, Chiou CA, Walsh HL, Tolentino J, Wester ST, Freitag SK, Douglas RS. The Rate of Re-treatment in Patients Treated with Teprotumumab: A Multicenter Study of 119 Patients with 1 Year of Follow-up. Ophthalmology. 2025 Jan;132(1):92-97

and a [redacted]% rebate for use above the tier 2 expenditure cap should apply from the second year of listing.

13.6 The PBAC recommended that teprotumumab should not be treated as interchangeable with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

13.7 The PBAC advised that teprotumumab is not suitable for prescribing by nurse practitioners. The PBAC advised that teprotumumab is suitable for prescribing by medical practitioners only.

13.8 The PBAC advised the Early Supply Rule should not apply.

13.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for teprotumumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies on the basis of superior comparative effectiveness to standard of care;

b) The treatment is expected to address a high and urgent unmet clinical need due to the lack of treatment options for patients with active MS TED;

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

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

Outcome:
Recommended

14 Recommended listing

Add new item:

Initial Restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TEPROTUMUMAB					
Teprotumumab 500 mg injection, 1 vial	NEW (public) NEW (private)	3	3	0	Tepezza
Restriction Summary / Treatment of Concept:					
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒ Medical Practitioners					
Restriction type: ☒ Authority Required (telephone/electronic) [new listing]					
Authority type: ☒ Non-complex Authority Required (non-CAR)					

Administrative Advice: No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Severity: Moderate-to-severe
Condition: Thyroid eye disease
Indication: Active Moderate-to-severe thyroid eye disease
Treatment Phase: Initial treatment
Clinical criteria:
Patient must not have previously received PBS-subsidised treatment with this drug for this condition; OR
Patient must be both: (i) undergoing re-treatment with this drug for this condition (ii) have demonstrated response to previous PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must have a clinical activity score (CAS) of three or more for the most severely affected eye,
AND
Clinical criteria:
Patient must have two or more of the following: (i) Proptosis ≥3 mm above normal for race and gender, (ii) Lid retraction ≥2mm, (iii) Moderate to severe soft-tissue involvement, (iv) inconstant or constant diplopia
AND
Clinical criteria:
Patient must be at least 18 years of age
~~**Clinical criteria:**~~
~~Patient must not have previously failed PBS-subsidised therapy with this drug for this condition~~
Treatment criteria:
Must be treated by a specialist physician experienced in the treatment of thyroid eye disease
Prescribing Instructions: The following must be provided at the time of application and documented in the patient's medical records for the first prescription only:*'* (i) Baseline clinical activity score (CAS) (ii) *Confirmation* of the presence of Thyroid Eye Disease (this includes evidence of two or more of the following: (i) Proptosis ≥3mm above normal for race and gender, (ii) Lid retraction ≥2mm, (iii) Moderate to severe soft-tissue involvement, (iv) Inconstant or constant diplopia)
Prescribing Instructions: Increased maximum amounts may only be authorised where a patient's weight is greater than 150 kg.
Prescribing Instructions: *After completing 8 doses in total of PBS subsidised treatment with teprotumumab, a patient may be eligible for re-treatment through the initial treatment phase only, if a response to treatment was previously demonstrated.*
Caution: Assess patients' hearing before, and routinely during and after treatment, including use of audiograms where clinically warranted. *If significant hearing loss is experienced while receiving treatment with this drug for this condition, treatment discontinuation is advised. See also TGA approved Product Information*
Caution: Teprotumumab is contraindicated in pregnancy. Women of childbearing potential should have a negative pregnancy test before starting treatment with *teprotumumab*~~*TEPEZZA*~~, and monthly during treatment and for 6 months after cessation of treatment. If the patient becomes pregnant during treatment *teprotumumab*~~TEPEZZA~~ should be discontinued. See also *TGA approved* Product Information.

Continuing Restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TEPROTUMUMAB					
Teprotumumab 500 mg injection, 1 vial	NEW (public) NEW (private)	6	6	6	Tepezza
Restriction Summary / Treatment of Concept:					
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒ Medical Practitioners					
Restriction type: ☒ Authority Required (Streamlined) [new code]					
Authority type: ☒ Non-complex Authority Required (non-CAR)					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Special Pricing Arrangements apply					
Indication: Active Moderate-to-severe thyroid eye disease					
Treatment Phase: Continuing treatment					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					
Treatment criteria:					
Must be treated by a specialist physician experienced in the management of thyroid eye disease; or					
Must be treated by a medical practitioner in consultation with a specialist physician experienced in the management of thyroid eye disease					
Prescribing Instructions: Increased maximum amounts may only be authorised where a patient's weight is greater than 150 kg.					
Prescribing Instructions: *After completing 8 doses in total of PBS subsidised treatment with teprotumumab, a patient may be eligible for re-treatment through the initial treatment phase only, if a response to treatment was previously demonstrated.*					
Assess patients' hearing before, and routinely during and after treatment, including use of audiograms where clinically warranted. *If significant hearing loss is experienced while receiving treatment with this drug for this condition, treatment discontinuation is advised. See also TGA approved Product Information*					
Teprotumumab is contraindicated in pregnancy. Women of childbearing potential should have a negative pregnancy test before starting treatment with *teprotumumab*~~TEPEZZA~~, and monthly during treatment and for 6 months after cessation of treatment. If the patient becomes pregnant during treatment *teprotumumab*~~TEPEZZA~~ should be discontinued. See also *TGA approved* Product Information.					

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

15 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.

16 Sponsor's Comment

The sponsor had no comment.