

## 7.01 ADALIMUMAB,

**Injection 20 mg in 0.2 mL, pre-filled syringe,  
Injection 40 mg in 0.4 mL, pre-filled syringe,  
Injection 40 mg in 0.4 mL, pre-filled pen  
Injection 80 mg in 0.8 mL, pre-filled syringe,  
Injection 80 mg in 0.8 mL, pre-filled pen  
Humira<sup>®</sup>,  
AbbVie Pty Ltd.**

### 1 Purpose of submission

- 1.1 The Standard Re-entry resubmission requested a General Schedule, Authority Required (Telephone/Online) listing for adalimumab for the treatment of patients with vision-threatening non-infectious uveitis.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo.

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

Component	Description
Population	<u>Vision threatening non-infectious uveitis</u> <sup>a</sup>
Intervention	Adalimumab 80 mg injection (given as 1 x 80 mg in 0.8 mL or 2 x 40 mg in 0.4 mL pre-filled syringe or cartridge), followed by 40 mg in 0.4 mL pre-filled syringe or cartridge every other week, starting one week after the initial dose. <sup>b</sup> For paediatric patients an initial loading dose of adalimumab 40 mg injection (given as 1 x 40 mg in 0.4 mL pre-filled syringe or cartridge or 2 x 20 mg in 0.2 mL pre-filled syringe) for patients < 30 kg or 80 mg injection (given as 1 x 80 mg in 0.8 mL or 2 x 40 mg in 0.4 mL pre-filled syringe or cartridge) for patients ≥ 30 kg may be administered one week prior to the start of fortnightly therapy at a dose based on body weight: <sup>b,c</sup> <ul style="list-style-type: none"> <li>&lt; 30 kg: adalimumab 20 mg in 0.2 mL pre-filled syringe every other week</li> <li>≥ 30 kg: adalimumab 40 mg in 0.4 mL pre-filled syringe or cartridge every other week</li> </ul>
Comparator	Current best supportive care: high dose oral corticosteroids (> 7.5 mg/day) with or without an immunomodulatory agent.
Outcomes	Time to treatment failure (inflammatory uveitic flare) analysed using a composite of 4 components: inflammatory chorioretinal and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity.
Clinical claim	Adalimumab is superior to best supportive care (BSC) in patients with non-infectious uveitis in terms of efficacy and is comparable with best supportive care in terms of safety.

Source: Table1-1, p31 of the submission. Para. 2.1 pp1-4, adalimumab March 2017 PBAC meeting.

AC = anterior chamber; mg = milligram; mL= millilitre; VH = vitreous haze

a Population in the March 2017 submission was described as “Ocular inflammation of a severity that is vision threatening” with suggestions and additions proposed by the Secretariat to the requested listing as “Vision threatening”.

b Intervention was the ‘new’ formulation manner of administration and form requests: Injection, 80mg in 0.8mL pre-filled syringe; Injection, 40mg in 0.4mL pre-filled syringe, 2; Injection, 20mg in 0.2mL pre-filled syringe (Adalimumab, PSD, December 2017; July 2018; November 2019, PBAC meeting).

c Population in the March 2017 submission was in adults.

Underline denotes changes compared with the previous submission (March 2017).

## 2 Background

### Registration status

- 2.1 Adalimumab was Therapeutic Goods Administration (TGA) registered on 26 October 2016 for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.
- 2.2 The TGA-approved indications for adalimumab also include: rheumatoid arthritis, juvenile idiopathic arthritis (JIA), enthesitis-related arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease in adults and children ( $\geq 6$  years), ulcerative colitis, psoriasis in adults and children and hidradenitis suppurativa in adults and adolescents (from 12 years of age).
- 2.3 TGA status at time of PBAC consideration (paediatric population): The Delegate’s Overview is not anticipated until September 2024, with registration expected around 31 December 2024.

### Previous PBAC consideration

- 2.4 The PBAC previously considered adalimumab for this indication in March 2017. Table 2 summarises the key matters of concern highlighted at the March 2017 meeting.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed the previous concern
PBS restriction	“The proposed restriction ...may allow less restrictive access to adalimumab than current restrictions for systemic diseases (e.g., the restriction for rheumatoid arthritis includes failure of at least two DMARDs). The use in patients with uveitis and systemic disease is clinically appropriate but may represent an avenue for leakage around existing restrictions” (para. 2.4, ADA, PSD, March 2017 PBAC meeting).	Not addressed.  Systemic disease was not explicitly excluded in the treatment algorithm or proposed PBS restriction.  The evaluation considered it may be clinically inappropriate to exclude patients with systemic disease. Currently biosimilars are streamlined authorities for subsequent continuing therapy for multiple indications.  The ESC considered the risk of leakage to other indications was low.  A risk-sharing arrangement was not proposed in the resubmission.
	“The PBAC noted the advice from the Royal Children’s Hospital Melbourne and that due to different dosing requirements a separate PBS restriction would be required if a paediatric listing was pursued (para. 7.3 ADA, PSD, March 2017 PBAC meeting).	Not addressed.  A separate paediatric PBS listing was not proposed. There are differences in typical disease manifestations/phenotypes and considerations for use of oral corticosteroids between adult and paediatric patients that merit further consideration.
Ocular complications	The PBAC noted uncertainties remain around the extrapolation of the efficacy of the surrogate (flares) to the efficacy against	Not addressed.

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Component	Matter of concern	How the resubmission addressed the previous concern
	<p>downstream complications, such as cataracts, visual disturbance, glaucoma and blindness. The PBAC noted that the components of the composite measure are normally used in clinical practice to assess ocular inflammation. However, the extrapolation of the relationship between flare and ocular complication was likely to be overestimated, strongly favouring adalimumab (paras 6.10, 7.8, ADA, PSD, March 2017 PBAC meeting).</p> <p>“The PBAC noted there is no long term use of corticosteroids in the trials so there is no direct data to inform the model of the relative efficacy or safety of adalimumab versus chronic corticosteroid use. The PBAC agreed with the ESC that the forced corticosteroid taper schedules may have overestimated the treatment effect of adalimumab” (para. 7.5, ADA, PSD, March 2017 PBAC meeting),</p>	<p>The resubmission did not present clinical evidence directly linking adalimumab treatment with ocular complications. A meta-analysis conducted during the evaluation of TEAEs relating to ocular disorders or complications between the adalimumab and placebo arms in the VISUAL I and VISUAL II trials, using a random effects model, found no difference in relative risk, as the bounds of the 95% CI included 1 (pooled relative risk: 1.00, 95% CI: 0.79, 1.27). Further, clinical evidence demonstrating a link between flares and downstream ocular complications was not presented. The lack of demonstrating a clear benefit in downstream ocular complications or link between active flares and ocular complications has implications for the reliability of the results of the economic model.</p> <p>The ESC considered a link between repeat flares and downstream ocular complications was biologically plausible but difficult to quantify reliably for the economic model.</p> <p>Partially addressed.</p> <p>The OLE VISUAL III and the supplementary observational studies did not include forced steroid taper. However, the clinical efficacy in the economic evaluation was still based on the VISUAL I and II trials, where there was forced corticosteroid taper schedules, however it was applied to both treatment arms.</p> <p>The ESC agreed with the evaluation and considered the design of the randomised trials precluded a direct assessment of the comparative effectiveness of adalimumab and the comparator and was a significant source of uncertainty.</p>
Immunomodulatory therapy usage at baseline	<p>“The PBAC noted only a proportion of patients in VISUAL I and VISUAL II were taking immunomodulating therapy at baseline (approximately 31% and 47%, respectively), and there was no evaluation of treatment effect modification by use of immunomodulatory agents” (para. 7.6, ADA, PSD, March 2017 PBAC meeting).</p>	<p>Partially addressed.</p> <p>Based on the subgroup analysis presented in the VISUAL III study CSR, the proportions of patients in quiescence among those with vs. without immunomodulatory therapy usage at baseline were similar (83.1% vs. 86.0% at week 150, respectively) (VISUAL III study CSR). However, the VISUAL III study was not designed, powered, or analysed to detect a difference in treatment effect based on prior immunomodulatory therapy.</p> <p>The ESC considered the impact of immunomodulatory therapy on the efficacy of adalimumab was uncertain, and considered that this remained a matter of concern, noting that</p>

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Component	Matter of concern	How the resubmission addressed the previous concern
		clinical criteria of the restriction requires uncontrolled disease despite use of immunomodulator therapy.
Reason for treatment failure	“.... the reasons for treatment failure varied across the VISUAL I and VISUAL II trials e.g. the most cited reason for treatment failure in the placebo arm in VISUAL I was vitreous haze, whereas in VISUAL II vitreous haze was the least cited reason” (para. 7.7, ADA, PSD, March 2017 PBAC meeting).	Not addressed.  The resubmission did not present new evidence confirming the reasons behind the treatment failure.
Economic evaluation	“The PBAC noted that...the effect of treatment was likely to be over-estimated because the less conservative estimate of treatment effect (from VISUAL 1) was selected over the more conservative estimate from VISUAL 2 (HR 0.57), and because the treatment effect on uveitis flares was assumed to be a perfect surrogate for the treatment effect on uveitis-attributable complications. The PBAC considered the model should have factored both a more conservative estimate of the effect of treatment on flares, and a more conservative assumption of the relationship between the effect of treatment on acute flares and the effect of treatment on uveitis-attributable complications” (para. 7.13, ADA, PSD March 2017 PBAC meeting).	Partially addressed.  Efficacy of ADA in the economic evaluation was based on time to treatment failure in both the VISUAL I and VISUAL II trials (pooled HR 0.53, Figure 1). However, the forced corticosteroid taper schedules may have overestimated the treatment effect of adalimumab in clinical practice.  The economic evaluation continued to include a perfect relationship (“link coefficient”) to capture the proportion of ocular complications avoided relative to the number of flares avoided. Base case = 1 (assumed) SA = 0.85 (Leal et al. 2022) <sup>a</sup>  Probabilities of ocular complications adjusted for the risk of ocular complications without uveitis were estimated.  The resubmission did not provide clinical evidence supporting the direct link between adalimumab treatment and ocular complications, or sequentially link active flares to ocular complications in the economic model.  The ESC considered the link coefficient relationship of 1:1 likely overestimated the adalimumab treatment effect due to the inherent uncertainty of downstream events.
	The PBAC previously considered that “As there was considerable uncertainty between flares and ocular complications, the PBAC did not consider the lifetime time horizon appropriate and that it significantly overestimated the cost effectiveness of adalimumab. The PBAC suggested important differences in costs and outcomes would be captured in a 10 year time horizon given majority of ocular complications are expected to occur within 2–5 years” and considered that a major resubmission “should present a revised economic	Not addressed.  No change but explored the impact of a time horizon of 10 and 20 years in one-way sensitivity analyses.  The ESC considered that given the uncertainty of the magnitude of the relationship between the surrogate outcome (flares) and modelled ocular complications, it may be reasonable to explore a shorter time horizon to reduce uncertainty; but acknowledged a shorter time horizon would

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Component	Matter of concern	How the resubmission addressed the previous concern
	model...including...a revised time horizon of 10 years” (paras. 7.14 and 7.16, ADA, PSD, March 2017 PBAC meeting).	exclude plausible ongoing quality of life benefits associated with avoiding ocular complications.
	The PBAC previously considered the model should include both the benefits and harms of corticosteroid use.  The adverse events of adalimumab also need to be included in the model (para. 7.15, ADA, PSD March 2017 PBAC meeting).	Not addressed.  Disutilities related to OCS adverse events were removed from the economic model. The change in EQ-5D scores from baseline either favoured ADA or were not statistically significant in the trials (VISUAL I: 0.04, p= 0.04, VISUAL II: 0.00, p= 0.836). The EQ-5D scores would have captured the impact of any differences between ADA and OCS in adverse events on utilities in the short term, however any differences may have been underestimated in the long term due to forced tapering of OCS in the trials. The effect of re-including disutilities associated with OCS adverse events on the ICER was minimal.

Source: Para. 2.4, 6.10, 7.5, 7.3 and Table 7 ADA, PSD, March 2017, PBAC meeting; pp 39-40, 45-48, 98, 130, 158, 160, 162 of the submission.

ADA = adalimumab; CI = confidence interval; CSR = clinical study report; DMARDs = disease-modifying anti-rheumatic drugs; bDMARD = biological disease-modifying anti-rheumatic drugs; ESC = Economic Sub-Committee; EQ-5D = EuroQol 5 Dimension; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IFX = infliximab; OCS = oral corticosteroids; OLE = open label extension; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; SA = sensitivity analysis; TEAE = treatment-emergent adverse events

a Leal (2022) retrospectively reviewed 51 patients with non-infectious uveitis (102 affected eyes) in the UK. The study found that 13 out of 51 patients (20 eyes; unilateral in 6 patients) experienced treatment failure after 12 months, after starting adalimumab. Of the 20 eyes that experienced treatment failure, 17 (85%) eyes experienced failure because of worsening visual acuity (7 eyes due to macular oedema, 4 eyes due to cataract development, 6 eyes due to unspecified and miscellaneous reasons such as advanced glaucoma and corneal decompensation).

### 3 Requested listing

3.1 The restrictions requested in the submission are presented below and have not been updated with Secretariat comments as the PBAC considered additional work will be required to finalise the restrictions. For brevity reasons, an abbreviated version of the requested restrictions is presented below (proposed subsequent continuing and grandfather restrictions are not presented).

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpt	Available brands
<b>ADALIMUMAB</b>					
<b>Initial Treatment</b>					
Adalimumab Injection, 80mg in 0.8mL pre-filled syringe	\$676.79	1	1	0	Humira, AbbVie Pty Ltd
Adalimumab Injection, 80mg in 0.8mL pre-filled pen	\$676.79	1	1	0	Humira, AbbVie Pty Ltd
Adalimumab Injection, 40mg in 0.4mL pre-filled syringe, 2	\$676.79	1	2	6	Humira, AbbVie Pty Ltd
Adalimumab Injection, 40mg in 0.4mL pre-filled pen, 2	\$676.79	1	2	6	Humira, AbbVie Pty Ltd
Adalimumab Injection, 20mg in 0.2mL pre-filled syringe, 2	\$706.70	1	2	6	Humira, AbbVie Pty Ltd

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Continuing Treatment					
Adalimumab Injection, 40mg in 0.4mL pre-filled syringe, 2	\$676.79	1	2	5	Humira, AbbVie Pty Ltd
Adalimumab Injection, 40mg in 0.4mL pre-filled pen, 2	\$676.79	1	2	5	Humira, AbbVie Pty Ltd
Adalimumab Injection, 20mg in 0.2mL pre-filled syringe, 2	\$706.70	1	2	5	Humira, AbbVie Pty Ltd

Source: Table1-7, p45; Table 3-12, p170; pp202-203 of the submission

<b>Category / Program:</b> General Schedule
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required (Telephone), <input checked="" type="checkbox"/> Authority Required (Electronic)
<b>Severity:</b> Vision threatening
<b>Condition:</b> Non-infectious uveitis
<b>Indication:</b> Non-infectious uveitis
<b>Treatment phase:</b> Initial
<b>Treatment criteria:</b> Must be treated by or in consultation with an ophthalmologist, rheumatologist or immunologist with expertise in uveitis
<b>Clinical criteria:</b>
Patient must have non-infectious uveitis that is vision threatening with the diagnosis confirmed by an ophthalmologist, rheumatologist, or immunologist;
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have failed to achieve an adequate response to corticosteroid therapy in combination with at least 1 immuno-suppressive agent or flared when corticosteroid therapy was tapered to a dose of $\leq 7.5$ mg/day while on immunomodulatory therapy;
<b>OR</b>
<b>Clinical criteria:</b>
Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contra-indication to corticosteroid and/or immunomodulatory therapy;
<b>AND</b>
<b>Clinical criteria:</b>
Treatment must not exceed 24 weeks under this restriction
<b>Population criteria:</b>
Vision threatening disease is defined as at least 1 of the following:
a) A decrease in visual acuity of at least 10 letters using an ETDRS chart or equivalent;
b) A two-step increase in anterior chamber cells or vitreous haze;
c) New retinal vasculitis;
d) New retinal or choroidal lesions;
e) Other signs of disease progression including visual field changes or electroretinogram changes.

<b>Category / Program:</b> General Schedule
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required (Telephone) <input checked="" type="checkbox"/> Authority Required (Electronic)
<b>Severity:</b> Vision threatening
<b>Condition:</b> Non-infectious uveitis
<b>Indication:</b> Non-infectious uveitis
<b>Treatment phase:</b> Continuing treatment
<b>Treatment criteria:</b> Must be treated by or in consultation with an ophthalmologist, rheumatologist or immunologist with expertise in uveitis
<b>Clinical criteria:</b>
Patient must have a documented history of non-infectious that is vision threatening;
<b>AND</b>
<b>Clinical criteria:</b>

Patient must have previously been issued with a prescription for this drug for this condition;
<b>AND</b>
<b>Clinical criteria:</b>
Patient has demonstrated a clinical response as defined by:
<ul style="list-style-type: none"> <li>a) Sustained reduction in inflammation defined as a 2 step decrease from baseline in Standardisation of Uveitis Nomenclature (SUN) criteria for anterior chamber or vitreous haze; or</li> <li>b) Sustained quiescence of inflammation defined as Standardisation of Uveitis Nomenclature (SUN) criteria <math>\leq 0.5+</math> anterior chamber or vitreous haze, absence of active vitreous or retinal lesions or vitreous cells; or</li> <li>c) Sustained corticosteroid sparing effect, allowing reduction in prednisone to <math>&lt; 7.5</math>mg daily; or</li> <li>d) Reduction in frequency of ocular attacks to <math>\leq 1</math>/year (patients with Behcet's disease only)</li> </ul>
<b>AND</b>
<b>Clinical criteria:</b>
Treatment must not exceed 24 weeks under this restriction
<b>Population criteria:</b>
Vision threatening disease is defined as at least 1 of the following: <ul style="list-style-type: none"> <li>a) A decrease in visual acuity of at least 10 letters using an ETDRS chart or equivalent;</li> <li>b) A two-step increase in anterior chamber cells or vitreous haze;</li> <li>c) New retinal vasculitis;</li> <li>d) New retinal or choroidal lesions;</li> <li>e) Other signs of disease progression including visual field changes or electroretinogram changes.</li> </ul>
Patients are eligible to receive an additional 24 weeks of treatment with this drug providing they demonstrate a response as described above.

3.2 The resubmission proposed a dispensed price for maximum quantity (DPMQ) of \$676.79 for initial treatment 1 x 80 mg or initial and continuing treatment 2 x 40 mg; and \$706.70 initial and continuing treatment 2 x 20 mg. This differed from the DPMQ applied in the economic model and financial estimates (\$), which the resubmission calculated based on a proposed flat ex-manufacturer price of \$ per script for the 20 mg, 40 mg and 80 mg strengths, plus an assumed % future price reduction from price disclosure and a lower wholesale margin of \$ for the 40 mg and 80 mg scripts. The price disclosure-related assumptions were speculative at time of submission as price reductions through this policy cannot be prospectively determined. The resubmission stated that a lower indication-specific price will be incorporated into a weighted price, using the previously agreed method, if the approved ex-manufacturer price (AEMP) is higher than the indication price at the time of listing. Price disclosure related reductions were finalised prior to PBAC consideration, with a final AEMP of \$505.95 for the 2 x 40 mg form of adalimumab.

3.3 The proposed PBS restriction included an additional population compared to the March 2017 submission: children aged  $\geq 2$  years old. However, the Delegate's Overview for the paediatric indication is not anticipated until September 2024, with registration expected around 31 December 2024 (6 months after PBAC consideration). Advice from the Royal Children's Hospital Melbourne (paragraph [para.] 7.3, adalimumab, Public Summary Document [PSD], March 2017 PBAC meeting) recommended that due to different dosing requirements, a separate PBS restriction would be required if a paediatric listing was pursued. A separate PBS listing for the paediatric population was not proposed. The PBAC noted a restriction that can appropriately define the criteria for both populations requires consideration when finalising the restriction criteria.

- 3.4 The resubmission proposed “Vision threatening” severity and not “Ocular inflammation of a severity that is vision threatening”. This is aligned with the suggestions and additions proposed by the Secretariat to the requested listing restrictions accepted by the PBAC (para. 2.1 adalimumab, PSD, March 2017 PBAC meeting).
- 3.5 The evaluation noted that the resubmission removed “Patient has severe, vision-threatening ocular inflammation requiring rapid control” from the clinical criteria.
- 3.6 The proposed PBS indication is ‘Vision threatening non-infectious uveitis’. As ‘vision threatening’ is potentially open to interpretation, the ESC considered that it may be appropriate to amend the PBS indication to ‘Non-infectious uveitis’. The severity of the condition and requirement for it to be vision threatening is outlined through the criteria in the restriction.
- 3.7 The proposed PBS restriction requested a slightly expanded population compared to that requested in the March 2017 submission, the clinical trial evidence, and the TGA indication that included uveitis of no specific anatomical location. The key clinical trials (VISUAL I and II) excluded ‘isolated anterior non-infectious uveitis’ in adults. The TGA indication included ‘pan-uveitis’ but did not explicitly mention ‘anterior uveitis’ in adults. Adults with anterior uveitis typically achieve disease quiescence with a short-burst corticosteroid. Biologic agents may not be clinically necessary or used for adults with anterior uveitis only. The resubmission removed the reference to the anatomical location from the patient definition. The ESC considered anatomical location of disease was a relevant clinical consideration because of the relationship between location and clinical manifestations of non-infectious uveitis, including severity of symptoms, duration of flare and predictors of response to corticosteroids and conventional therapies, however noted the manifestations of disease often differed between adult and paediatric patients.
- 3.8 The proposed PBS restriction redefined vision-threatening disease as a decrease in visual acuity of 10 (not 15) letters on Early Treatment of Diabetic Retinopathy Study (ETDRS) (in addition to other criteria). This was based on clinical advice that a decrease of 15 letters is catastrophic, rarely seen in practice, and no longer accepted as clinically appropriate. The ESC and PBAC considered this was appropriate.
- 3.9 The resubmission suggested that once uveitis had been held in corticosteroid-free quiescence for at least 2 years, adalimumab and other immunomodulatory therapy may be withdrawn. No maximum treatment duration was applied in the economic model. The ESC considered it may be reasonable to include criteria for the withdrawal of treatment after a period of corticosteroid-free quiescence after 1–2 years or another mechanism to attempt withdrawal of adalimumab, with the ability to recommence treatment if the condition recurs. The Pre-PBAC Response argued that due to the rare and often aggressive nature of disease, appropriate timing for tapered dosing is an individualised clinical decision and therefore restrictions which mandate withdrawal at a certain timepoint are clinically inappropriate, may decrease the

success of treatment and create additional stress and anxiety for patients. The PBAC agreed it was appropriate for the timing of attempting to withdraw adalimumab to be a decision for clinicians.

- 3.10 For the diagnosis and treatment (directly or in consultation) of non-infectious uveitis that is vision threatening, the resubmission proposed including a rheumatologist or immunologist (in addition to an ophthalmologist) to the proposed restriction. The ESC considered that all patients with non-infectious uveitis would be likely to have seen an ophthalmologist, and the role of rheumatologists and immunologists in management of non-infectious uveitis was unclear.
- 3.11 The proposed PBS restriction population in the resubmission was adalimumab for the treatment of non-infectious uveitis after the failure of oral corticosteroids (OCS) with or without an immunomodulatory agent. These patients would become PBS eligible for biologic therapy potentially earlier than currently required under the PBS restrictions for other systemic immune diseases (e.g. the restriction of rheumatoid arthritis includes the failure of at least 2 disease-modifying anti-rheumatic drugs [DMARDs]). The use in patients with uveitis and systemic disease is clinically appropriate but may represent an avenue for leakage around existing restrictions (para. 2.4, adalimumab, PSD, March 2017 PBAC meeting). The ESC noted this, but considered the risk of leakage to other indications was low.
- 3.12 The PBS restriction was not consistent with the clinical trial evidence:
- The resubmission requested a slightly expanded population compared to that requested in the March 2017 submission, the clinical trial evidence, and the TGA indication by removing the reference to specific anatomical locations. The key clinical trials (VISUAL I and II) excluded ‘isolated anterior non-infectious uveitis’ in adults.
  - The key paediatric trials (ADJUVITE and SYCAMORE) were conducted in patients with juvenile idiopathic arthritis (JIA) with ADJUVITE also including idiopathic uveitis patients. Clinical evidence was not presented for patients with other systemic immune diseases. Furthermore, both SYCAMORE and ADJUVITE trials required patients to have failed methotrexate therapy, and in the ADJUVITE trial the median daily dose of corticosteroids was 5 mg and under the comparator threshold of >7.5mg of corticosteroid.<sup>1</sup> The ESC considered that the proposed restriction for adults regarding OCS use was likely not appropriate for paediatric patients.

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

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<sup>1</sup> Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, Belot A, Kodjikian L, Monnet D, Weber M, Elie C, Bodaghi B; ADJUVITE Study Group. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis.* 2018 Jul;77(7):1003-1011.

## 4 Population and disease

- 4.1 Non-infectious uveitis is a rare but serious inflammatory eye disease that is one of the leading causes of vision loss in adults and children. Non-infectious uveitis goes through phases of active inflammation or flare where patients are aware of ocular discomfort, pain, redness, or blurred/decreased vision. Disease flare is separated by periods of variable length when the inflammation has settled, and the patient is asymptomatic. Affected patients are at high risk of ocular complications including cataracts, glaucoma, cystoid macular oedema (CMO), retinal detachment, macular scarring, optic neuropathy, macular ischaemia, and permanent vision loss. In most cases of uveitis, visual morbidity usually does not occur from a single inflammatory flare; rather, recurrent episodes of inflammation cause cumulative eye damage. Vision loss associated with non-infectious uveitis has a negative impact on quality of life and activities of daily living. In Australia, the prevalence of adult uveitis was estimated to be 36.27 cases/100,000 persons, and the prevalence of paediatric uveitis was estimated to be 30/100,000 children.<sup>2</sup>
- 4.2 First-line treatment of vision-threatening non-infectious uveitis is high-dose (oral or intravenous) systemic corticosteroids. The corticosteroid dose will then be decreased or tapered. The goal of treatment is the induction of durable, corticosteroid-free quiescence and preservation of vision. Immunomodulatory therapy may then be introduced to control inflammation and prevent the patient from flaring.
- 4.3 The resubmission clinical management algorithm positioned adalimumab as an alternative treatment for patients who have failed, or who are intolerant or contraindicated to treatment with a corticosteroid and an immunomodulatory therapy. This was unchanged from the March 2017 submission (para. 4.2, adalimumab, PSD, March 2017 PBAC meeting).
- 4.4 The clinical management algorithm for adults included the withdrawal of immunotherapy if corticosteroid-free quiescence was achieved for at least 2 years. However, the TGA product information (PI) stated that “It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis” (TGA draft PI, adalimumab 27 September 2023). The open label extension study in adults, VISUAL III, followed patients up to week 150, when approximately 50% of patients remained in the study.<sup>3</sup> Furthermore, Eurelings et al. (2022) reported the median treatment duration until discontinuation was 3.2 years and the median time

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<sup>2</sup> Hart CT, Zhu EY, Crock C, Rogers SL, & Lim LL. Epidemiology of uveitis in urban Australia. *Clin Exp Ophthalmol*, 2019;47(6):733-740.

<sup>3</sup> Suhler EB, Jaffe GJ, Fortin E, Lim LL, Merrill PT, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Van Calster J, Cimino L. Long-term safety and efficacy of adalimumab in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology* 2021;128(6):899-909.

to the first relapse was 3.4 years (range, 0-13 years).<sup>4</sup> This would suggest that a significant proportion of patients would be treated for more than 2 years.

- 4.5 There was no specific clinical management algorithm presented for paediatric patients.
- 4.6 Adalimumab is a tumour necrosis factor alfa (TNF- $\alpha$ ) inhibitor that binds to TNF- $\alpha$  and neutralises its biological function by blocking its interaction with the p55 and p75 cell surface TNF- $\alpha$  receptors. TNF- $\alpha$  is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Adalimumab also modulates biological responses that are induced or regulated by TNF- $\alpha$ , including changes in the levels of adhesion molecules responsible for leukocyte migration. TNF- $\alpha$  has been shown to play a role in the perpetuation of inflammation in uveitis by facilitating further leukocyte infiltration via adhesion molecule upregulation, macrophage activation, and dendritic cell maturation/survival.
- 4.7 Adalimumab co-administered therapies consist of high-dose OCS (>7.5 mg/day) with or without an immunomodulatory agent.

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

## 5 Comparator

- 5.1 The resubmission nominated best supportive care (BSC) as the comparator. The proposed comparator consisted of high-dose OCS (> 7.5 mg/day) with or without an immunomodulatory agent, such as methotrexate, mycophenolate mofetil or cyclosporine. The main argument provided in support of this nomination was that there are no currently reimbursed treatments on the PBS for the proposed population. The comparator was accepted by the PBAC in the March 2017 submission (para. 7.4, adalimumab, PSD, March 2017 PBAC meeting).
- 5.2 Intravitreal dexamethasone was PBS-listed for the treatment of non-infectious posterior segment uveitis in April 2018. Adalimumab was nominated as a secondary near-market comparator in the submission. However, the PBAC determined that dexamethasone implant and adalimumab are likely to be used in different populations (submission) (para. 5.3, dexamethasone, PSD, November 2017 PBAC meeting).
- 5.3 There are currently no other biologic agents PBS listed for the treatment of non-infectious uveitis.
- 5.4 The proposed PBS comparator in terms of the dose of corticosteroids may not be applicable to the paediatric population due to the risk of adverse events (AEs). There

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<sup>4</sup> Eurelings LEM, Missotten TOAR, van Velthoven MEJ, van Daele PLA, van Laar JAM, van Hagen PM, Thiadens AAHJ, Rombach SM. Long-Term Follow-up of Patients With Uveitis Treated With Adalimumab: Response Rates and Reasons for Discontinuation of Therapy. *Am J Ophthalmol.* 2022 Aug;240:194-204.

was essentially no corticosteroid use in the SYCAMORE trial<sup>5</sup> (instead the trial used methotrexate) and a 5 mg median dose of corticosteroids was used in the ADJUVITE trial. The SYCAMORE trial population was also refractory to methotrexate. The Australian Living Guideline for the Management of Juvenile Idiopathic Arthritis - Australia & New Zealand Musculoskeletal Clinical Trials Network, recommend in JIA associated uveitis, OCS (topical or systemic) use is limited by dose dependent complications such as cataracts and glaucoma. While in patients with JIA only, the role of glucocorticoids is unclear. Given the side-effects relating to long-term glucocorticoid use, it is generally accepted that they are not a long-term treatment option.<sup>6</sup> The Pre-Sub-Committee Response (PSCR) agreed with the evaluation that long-term use of high dose corticosteroids is clinically unacceptable due to the risk of AEs, particularly in children. The PSCR stated that while the variation in use of corticosteroids by age potentially impacts comparator selection, corticosteroids remain the only PBS funded treatment option in both populations, therefore a pragmatic approach has been taken in nominating a common comparator.

- 5.5 The comparator in the economic model of the March 2017 submission was “standard of care ( $\pm$  oral corticosteroid or OCS)”, which hereafter will be referred to as BSC ( $\pm$  OCS).

*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 clinician discussed the treatment algorithm and how non-infectious uveitis is managed before adalimumab is considered, and emphasised the ‘transformative’ benefits to patients. The clinician highlighted that many patients find OCS and immunomodulator therapy ineffective, and those treatments often at best delay ocular complications and are associated with a significant treatment burden. The clinician noted that adalimumab is highly effective at reducing flares and emphasised that there is a relationship between flares and later ocular complications which can include cataract and glaucoma surgery. The clinician considered that treatment with adalimumab would lead to important improvements in quality of life, and the OCS-sparing advantages of adalimumab for many patients would further add to these benefits.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (35), health care professionals (11) and organisations (4) via the Consumer Comments facility on the

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<sup>5</sup> The SYCAMORE trial included OCS  $<0.2\text{mg/kg}$  however only 6 patients from 90 were taking OCS at randomisation. (Hence the OCS dose for a 30kg child at a rate of  $0.2\text{mg/kg}$  would be 6 mg or 4 mg in a 20kg child less than the proposed  $>7.5\text{mg}$ ).

<sup>6</sup> An Australian Living Guideline for the Management of Juvenile Idiopathic Arthritis <https://app.magicapp.org/#/guideline/7562>

PBS website. The PBAC noted the comments from individuals included a number of people who have direct experience using adalimumab for non-infectious uveitis (typically through one of the existing access programs) and the family members of those who use or have used it. These comments discussed how adalimumab was tolerable, easy to use and had reduced their flares and allowed them to resume daily activities and live normal lives. Other comments from individuals discussed how adalimumab had turned an otherwise blinding disease into a treatable one with fewer complications, and highlighted the benefits of being able to reduce or discontinue corticosteroids and avoid the associated side effects. The PBAC also noted the comments from parents and families of children with uveitis highlighted how treatment with adalimumab was highly effective for reducing symptoms and allowed them to participate in all school activities, had additional flow-on benefits where there was co-existent joint and systemic symptoms, and allowed them to be taken off corticosteroids, which had additional benefits beyond the effectiveness of adalimumab.

- 6.3 The PBAC noted the input from health professionals describing the evidence of efficacy associated with adalimumab in non-infectious uveitis for those whose condition is not adequately controlled by first line therapies and for those in whom high and sustained doses of corticosteroids are required. The PBAC noted the input from health professionals also commented on the need for early intervention to limit irreversible ocular damage and highlighted the evidence of effectiveness in paediatric patients as well as adults.
- 6.4 The PBAC noted the input from specialist medical and health consumer organisations, including:
- The comments from the Australian Rheumatology Association (ARA) describing the role rheumatologists play in co-managing autoimmune conditions including non-infectious uveitis, and discussed the clinical place of adalimumab as an effective therapy in adults and children with severe or treatment-resistant disease. The input also commented that secure access to therapies like adalimumab through the PBS is critical to provide appropriate care to patients with non-infectious uveitis.
  - The comments from the Juvenile Arthritis Foundation Australia (JAFA) discussed that children with juvenile idiopathic arthritis have a high risk of co-existent uveitis, and highlighted the established benefits of adalimumab, which has changed a blinding disease in children and adolescents with JIA into a controllable condition, and argued the current treatment paradigm of using adalimumab after the failure of corticosteroids and immunomodulator therapies was not aligned with current clinical evidence.
  - The comments from The Royal Victorian Eye and Ear Hospital (RVEEH) described the organisation's strong support for the PBS listing of adalimumab for non-infectious uveitis, and discussed the clinic's experience with it for this indication,

with high response rates to treatment observed, along with a significant steroid-sparing effect and associated benefits to patients. The comments also discussed that while corticosteroids continue to be prescribed for severe and acute uveitis, their clinical experience indicates that prolonged use of these agents are associated with significant morbidity and a reduction in steroid use is a critical issue for these patients. The comments also highlighted the importance of effective agents which are steroid-sparing, and described adalimumab as a vital, vision saving therapy that reverses the disability associated with visual impairment, which enables patients to return to work and other meaningful roles in their lives.

- The comments from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) described it as essential that adalimumab be available on the PBS for patients with uveitis, and described the vision-threatening consequences of the condition, including cataracts, glaucoma, vitreous opacification, cystoid macula oedema, band keratopathy, hypotony and retinal detachment as some of the consequences that can occur due to under-treated uveitis. The comments also described the severe side effects of sustained corticosteroids and highlighted the need to limit systemic steroid exposure, and the clear evidence of effectiveness of adalimumab both for treating uveitis and as a steroid-sparing treatment option. The input stated it is likely that the enrolment in current access programs likely represents the majority of patients who would benefit from treatment with adalimumab.

6.5 The PBAC considered the comments from organisations, patients, family members and health professionals were informative and highlighted the significant impacts of non-infectious uveitis, the benefits of having adalimumab available as a treatment option for this condition, the drawbacks of current PBS-subsidised options and the need for a universally equitable access and funding mechanism. The Committee expressed its thanks to all those who provided comments for sharing their views and experiences.

### ***Clinical trials and studies***

6.6 The resubmission was based on the following adalimumab trials previously seen by the PBAC (para. 6.6, adalimumab, PSD, March 2017 PBAC meeting):

- One randomised trial comparing adalimumab (80 mg starting, subsequent 40 mg then fortnightly) with placebo in patients with flaring non-infectious intermediate, posterior or panuveitis: VISUAL I (N = 217).
- One randomised trial comparing adalimumab (80 mg starting, subsequent 40 mg then fortnightly) with placebo in patients with controlled non-infectious intermediate, posterior or panuveitis: VISUAL II (N = 226).

6.7 The resubmission was based on the following adalimumab trials previously not seen by the PBAC:

- One open label extension study (40 mg) in patients with non-infectious intermediate, posterior or panuveitis: VISUAL III (N = 424). Only the interim analysis of the VISUAL III study (a conference abstract) was previously considered by the PBAC.
- One randomised trial comparing adalimumab (24 mg/m<sup>2</sup> in patients aged < 13 years, 40 mg in the others, fortnightly) + methotrexate with placebo + methotrexate in patients ≥ 2 to 18 years with active JIA-associated uveitis refractory to methotrexate: SYCAMORE (N = 90).
- One randomised trial comparing adalimumab (20 mg or 40 mg, according to body weight) +/- methotrexate with placebo +/- methotrexate in patients ≥ 4 years old with chronic, active anterior uveitis associated with JIA or idiopathic, refractory to methotrexate and steroid therapy: ADJUVITE (N = 32).
- 18 supplementary non-randomised observational studies (13 relating to adult and 5 relating to paediatric uveitis patients) investigating adalimumab longer-term efficacy and safety including:
  - Eurlings et al. (2022), a retrospective cohort study investigating the response rates and reasons for discontinuation of adalimumab. Results from this study were used in the economic model.

6.8 Details of the trials and observational studies presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Randomised controlled studies</b>		
<b>Adult</b>		
VISUAL I (M10-877) NCT01138657	A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis - Including a Sub-study in Japanese Patients.	23 July 2015
	Jaffe GJ; Dick AD; Brézin AP; Nguyen QD; Thorne JE; Kestelyn P; Barisani-Asenbauer T; Franco P; Heiligenhaus A; Scales D and Chu DS. Adalimumab in Patients with Active Noninfectious Uveitis.	<i>New England Journal of Medicine</i> 2016; 375(10):932-943
	Jaffe GJ, Thorne JE, Scales D, Franco PJ, Tari S, Camez A, Song AP, Kron M, Barisani-Asenbauer T, & Dick AD. SAT0523 Adalimumab in Patients with Active, Non-Infectious Uveitis Requiring High-Dose Corticosteroids: the Visual-1 Trial.	<i>Annals of the Rheumatic Diseases</i> 2015;74(Suppl 2):849-850.
	Brezin A, Chen N, Tari S, Skup M, & Joshi A. THU0565 Clinical Relevance of Treatment Failure as Assessed by the 25-Item Visual Functioning Questionnaire in Patients with Intermediate-, Posterior-, and Pan-Uveitis: Results from The Visual-1 Trial.	<i>Annals of the Rheumatic Diseases</i> 2016; 75:396.
	Brezin AP, Dick AD, Jaffe GJ, Ohno S, Namba K, Goto H, Inomata N, Song AP, Kron M, Camez A, Tari S. THU0561 Adalimumab in Patients with Active and Inactive, Non-Infectious Uveitis: Visual I and Visual II Trials.	<i>Annals of the Rheumatic Diseases</i> 2016; 75:394-395.

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Rosenbaum JT, Fortin E, Lim LL, Goto H, Hashida N, Kron M, Song AP, Douglas K, Landewe R, Pathai S. 437 Long-term efficacy and safety of adalimumab in the ongoing noninfectious open-label VISUAL-III study in patients treated with placebo/adalimumab in VISUAL-I/II trials.</p> <p>Goto H, Zako M, Namba K, Hashida N, Kaburaki T, Miyazaki M, Sonoda KH, Abe T, Mizuki N, Kamoi K, Brézin AP. Adalimumab in active and inactive, non-infectious uveitis: global results from the VISUAL I and VISUAL II trials.</p> <p>Landewe R, van der Horst-Bruinsma I, Tari S, Florentinus S, Song A, Kron M, Pathai S, Rosenbaum J. THU0583 Quiescence in active and inactive non-infectious, intermediate, posterior, or panuveitis in patients treated with adalimumab: VISUAL I and VISUAL II trials.</p> <p>Suhler EB, Thorne JE, Mittal M, Betts KA, Tari S, Camez A, Bao Y, Joshi A. Corticosteroid-related adverse events systematically increase with corticosteroid dose in noninfectious intermediate, posterior, or panuveitis: post hoc analyses from the VISUAL-1 and VISUAL-2 trials.</p> <p>Sheppard J, Joshi A, Betts KA, Hudgens S, Tari S, Chen N, Skup M, Dick AD. Effect of adalimumab on visual functioning in patients with noninfectious intermediate uveitis, posterior uveitis, and panuveitis in the VISUAL-1 and VISUAL-2 trials.</p> <p>Merrill PT, Vitale A, Zierhut M, Goto H, Kron M, Song AP, Pathai S, Fortin E. Efficacy of adalimumab in non-infectious uveitis across different etiologies: a post hoc analysis of the VISUAL I and VISUAL II Trials.</p>	<p><i>International Journal of Rheumatic Diseases</i> 2017;20(S1):17–131</p> <p><i>Ocular Immunology and Inflammation</i> 2019;27(1):40-50.</p> <p><i>Annals of the Rheumatic Diseases</i> 2016;75(S2):403.</p> <p><i>Ophthalmology</i> 2017;124(12):1799-1807.</p> <p><i>JAMA Ophthalmology</i> 2017;135(6):511-518.</p> <p><i>Ocular Immunology and Inflammation</i> 2021;29(7-8):1569-1575.</p>
<p>VISUAL II M10-880 NCT01124838</p>	<p>A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Inactive Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis - Including a Sub-study in Japanese Patients</p> <p>Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, Schlaen A et al. Adalimumab for prevention of uveitic flare in patients with controlled non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial.</p> <p>Quan DN, Kurup SK, Merrill P, Sheppard J, Van Calster J, Dick AD, Jaffe G, Mackensen F, Rosenbaum JT, Schlaen A, Camez A. 1388 Adalimumab in patients with inactive, non-infectious uveitis requiring systemic treatment.</p>	<p>3 August 2015</p> <p><i>The Lancet</i> 2016;388(10050):1183-1192</p> <p><i>Arthritis &amp; Rheumatology</i> 2015;67(S10).</p>
<b>Paediatric</b>		
<p>SYCAMORE</p>	<p>A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial) Final Report</p> <p>A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial) Interim Report</p> <p>Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, Hardwick B, Hickey H, Hughes D, Woo P, Benton D. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis.</p> <p>Horton S, Jones AP, Guly CM, Hardwick B, Beresford MW, Lee RW, Dick AD, Ramanan AV. Adalimumab in Juvenile Idiopathic Arthritis–Associated Uveitis: 5-Year Follow-up of the Bristol Participants of the SYCAMORE Trial.</p>	<p>27 February 2018</p> <p>2 August 2017</p> <p><i>New England Journal of Medicine</i> 2017; 376(17):1637-1646.</p> <p><i>American journal of ophthalmology</i> 2019; 207:170-174.</p>
<p>ADJUVITE NCT01385826</p>	<p>THU0235 Adjuvite: A double-blind, randomized, placebo-controlled trial of adalimumab in juvenile idiopathic arthritis associated uveitis.</p>	<p><i>Annals of the Rheumatic Diseases</i> 2016; 75:273.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, Belot A, Kodjikian L, Monnet D, Weber M, Elie C, Bodaghi B; ADJUVITE Study Group. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis.	<i>Ann Rheum Dis.</i> 2018;77(7):1003-1011.
<b>Non-randomised studies</b>		
<b>Adult</b>		
VISUAL III M11-327 NCT01148225 Eurelings et al. (2022) Fabiani et al. (2018)	A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis Suhler EB, Adán A, Brézin AP, Fortin E, Goto H, Jaffe GJ, Kaburaki T, Kramer M, Lim LL, Muccioli C, Nguyen QD. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. Suhler EB, Jaffe GJ, Fortin E, Lim LL, Merrill PT, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Van Calster J, Cimino L. Long-term safety and efficacy of adalimumab in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis.	20 September 2018  <i>Ophthalmology</i> 2018;125(7):1075-1087.  <i>Ophthalmology</i> 2021;128(6):899-909.
Lee et al. (2018)	Lee JT, Yates WB, Rogers S, Wakefield D, McCluskey P, Lim LL. Adalimumab for the treatment of refractory active and inactive non-infectious uveitis.	<i>Br J Ophthalmol.</i> 2018;102(12):1672-1678
Llorenc et al. (2019)	Llorenç V, Cordero-Coma M, Blanco-Esteban A, Heras-Mulero H, Losada-Castillo MJ, Jovani-Casano V, Valls-Pascual E, Jodar-Marquez M, García-Aparicio Á, Fonollosa A, González-Guijarro JJ, Rodríguez-Melian L, Fernández-Prada M, Jerez-Fidalgo M, Hernandez-Garfella M, Esquinas C, Sainz-de-la-Maza M, Adán A; Biotherapies in Uveitis (BioÚvea) Study Group. Drug Retention Rate and Causes of Discontinuation of Adalimumab in Uveitis: Real-World Data from the Biotherapies in Uveitis (BioÚvea) Study Group.	<i>Ophthalmology.</i> 2020;127(6):814-825.
Maalouf et al. (2022)	Maalouf G, Andrillon A, Leclercq M, Sève P, Bielefeld P, Gueudry J, Sené T, Titah C, Moulinet T, Rouvière B, Sène D, Desbois AC, Domont F, Touhami S, Thibault T, El Chamieh C, Cacoub P, Kodjikian L, Biard L, Bodaghi B, Saadoun D. Lower Relapses Rate With Infliximab Versus Adalimumab in Sight-Threatening Uveitis: A Multicenter Study of 330 Patients.	<i>American Journal of Ophthalmology</i> 2022; 238:173-180.
Moll-Udina et al. (2020)	Moll-Udina AM, Miguel Escuder L, Hernanz I, Llorenç V, Fonollosa A, Cordero Coma M, Sainz de la Maza M, Espinosa G, González Guijarro JJ, Lopez Lopez F, Alba-Linero C, Hernández M, Martínez Costa L, Celdrán Vivancos D, Giral L, Artaraz J, Soler Bartrina P, Jódar Márquez M, García de Vicuña R, Esquinas C, Adán A. Adalimumab in Elderly Patients with Non-Infectious Uveitis. Safety and Efficacy.	<i>Ocular Immunology and Inflammation</i> 2021;29(7-8):1591-1598.
Park et al. (2020)	Park SE, Jun JW, Lee DH, Lee SC, Kim M. The Effect of Adalimumab in Korean Patients with Refractory Noninfectious Uveitis.	<i>Yonsei Med J.</i> 2021;62(2):177-181.
Pirani et al. (2020)	Pirani V, Pelliccioni P, De Turrís S, Rosati A, Franceschi A, Pasanisi P, Gesuita R, Nicolai M, Mariotti C. Intraocular Inflammation Control and Changes in Retinal and Choroidal Architecture in Refractory Non-Infectious Uveitis Patients after Adalimumab Therapy.	<i>J Clin Med.</i> 2020;13;9(2):510.
Pleyer et al. (2023)	Pleyer U, Al-Mutairi S, Murphy CC, Hamam R, Hammad S, Nagy O, Szepešy Z, Guex-Crosier Y, Julian K, Habot-Wilner Z, Androudi S. Impact of adalimumab in patients with active non-infectious intermediate, posterior, and panuveitis in real-life clinical practice: HOPE study.	<i>Br J Ophthalmol.</i> 2023;107(12):1892-1899.
Vallet et al. (2016)	Vallet H, Seve P, Biard L, Fraison JB, Bielefeld P, Perard L, Bienvenu B, Abad S, Rigolet A, Deroux A, Sene D, Perlat A, Marie I, Feurer E, Hachulla E, Fain O, Clavel G, Riviere S, Bouche A, Saadoun D. Infliximab Versus	<i>Arthritis &amp; Rheumatology</i> 2016;68(6):1522-1530.

Trial ID	Protocol title/ Publication title	Publication citation
	Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study from the French Uveitis Network.	
NCT02916017	HUMIRA Special Investigation (Long-term Treatment in Patients with Non-infectious Intermediate-, Posterior-, or Pan-uveitis)	2020
NCT03339102	Re-examination report for post-marketing surveillance (PMS) study of adalimumab (Humira®) for non-infectious intermediate, posterior, or panuveitis patients	2020
Say et al. (2021)	Say TL, Yang V, Fingret JM, et al. Adalimumab in patients with vision-threatening uveitis: real-world clinical experience.	<i>BMJ Open Ophthalmology</i> 2021;6:e000819.
<b>Paediatric</b>		
Alekseeva et al. (2012)	Alekseeva E, Mitenko E, Bzarova T, Valieva S, Isayeva K, Chomakhidze A, Chistyakova E, Sleptsova T. 1148 Adalimumab—Effective Control under Refractory JIA Associated Uveitis.	<i>American College of Rheumatology. ACR/ARHP Annual Meeting 2012</i> ;S493
Biliavska et al. (2017)	Biliavska IV, Kovalenko VM, Bortkevych OP, Garmish OO, Boyko YE, Omelchenko LI, Oshlyanska OA, Marushko TV, Bogmat LF, Shevchenko NS. THU0510 Ukrainian registry of JIA patients receiving biologics: implementation into clinical practice and recent data.	<i>Annals of the Rheumatic Diseases</i> 2017;76:399.
Gaidar et al. (2017)	Gaidar E, Kostik M, Dubko M, Masalova V, Serogodskaya E, Snegireva L, Nikitina T, Chasnyk V, Kalashnikova O, Isupova E. The evaluation of efficacy of adalimumab in juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis	<i>Pediatric Rheumatology</i> 2017;15(Supp1):P447
Simonini et al. (2013)	Simonini G, Taddio A, Cattalini M, Caputo R, de Libero C, Parentin F, Pagnini I, Lepore L, Cimaz R. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF- $\alpha$ therapy in childhood chronic uveitis.	<i>Pediatric Rheumatology</i> 2013;11(16):1-7
Tynjala et al. (2008)	Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, Lahdenne P. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis	<i>Rheumatology</i> 2008;47:339–344

Source: Table 2-2, pp58-65 of the submission; Attachment 2; VISUAL I CSR; VISUAL II CSR, SYCAMORE CSR.

Blue shading indicates data previously seen by the PBAC including the interim analysis of the VISUAL III study.

## 6.9 The key features of the direct randomised trials and studies are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Comparison / Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>ADULTS</b>						
Randomised trials of ADA vs. PBO (N=2)						
VISUAL I	217	ADA + BSC vs BSC vs R, M, DB 80 weeks	Low	NIIPPU with active (flaring) disease	Primary: Time to treatment failure (flare) <sup>b</sup> Secondary: change in AC cell grade, change in VH grade (NEI/SUN criteria), change in logMAR BCVA, time to OCT evidence of macular oedema, percent change in CRT in each eye, change in VFQ-25 composite score.	Pooled HR based on VISUAL I and VISUAL II trials, dosing (80 mg loading followed by 40 mg fortnightly), HR based on VISUAL I trial in sensitivity analysis.

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Trial	N	Comparison / Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
					Other: VFQ-25, sub scores, HADS, WPAI-SHP, EQ-5D, HRU	
VISUAL II	226	ADA + BSC vs BSC R, M, DB 80 weeks	Low	NIIPPU with inactive (controlled) disease	As above	
Non-randomised studies (N=14)						
VISUAL III	424	ADA, OL 78 weeks	High <sup>a</sup>	NIIPPU with active (flaring) and inactive (controlled) disease from the VISUAL I and VISUAL II trials	Primary: Quiescence <sup>e</sup> , Secondary: proportion of patients without a worsening of BCVA by ≥15 letters on the ETDRS in both eyes, percent change in CRT in each eye, change in VFQ-25 composite score, Proportion of patients achieving a ≥50% reduction in immunosuppression load. Other: WPAI-SHP, EQ-5D, HRU	AE (cost, discontinuations)
Eurelings et al. (2022)	341	ADA RT, MC, 4.9 yrs (median)	High <sup>a</sup>	Active/controlled NIIPPAU	ADA effectiveness (controlled disease/remission)	0.85 Discontinuations (AE/AnDA)
Fabiani et al. (2018)	107 (N=41 IFX; N=66 ADA)	ADA vs IFX RT, MC ADA: 26.45 mths (mean) IFX: 56.60 mths (mean)		Active NIIPPU + systemic disease	Decrease uveitis relapse	Not used
Lee et al. (2018)	22	ADA RT, MC 20.1 mths (mean)		Active/controlled NIIPPAU	Decrease corticosteroid dose	Not used
Llorenc et al. (2019)	392	ADA RT/Prospective, MC 49.07 mths (median)		Active/Controlled NIIPPAU	Drug retention rate	Not used
Maalouf et al. (2022)	330 (N=163 IFX; N=167 ADA)	ADA vs IFX RT, MC, 74.50 mths (median)		Active NIIPPAU <sup>c</sup>	Relapse rate with ADA and IFX	Not used
Moll-Udina et al. (2020)	41	ADA RT, MC, 156 mths		Elderly cohort (≥60 yrs) with NIIPPAU <sup>d</sup>	Changes in BCVA, inflammatory activity parameters, CRT	Not used

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Trial	N	Comparison / Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Park et al. (2020)	14	ADA RT, SC, 22.3 mths (median)		Active/refractory NIIPPU	Changes in VA, ACC, VH, CMT	Not used
Pirani et al. (2019)	18	ADA RT, SC, 22±8 mths (median)		Active chronic NIIPPU	Control of ocular inflammation	Not used
Pleyer et al. (2022)	149	ADA Prospective/RT, SC, 12 mths (median)		Active NIIPPU	Quiescence	Not used
Vallet et al. (2016)	160 (N=98 IFX vs. N=62 ADA)	ADA vs IFX RT, MC, 36 mths (median)		Active refractory NIIPPAU	Treatment response	Not used
NCT02916017	259	ADA Prospective		NIIPPU <sup>d</sup>	ADR	Not used
NCT03339102	158	ADA Prospective		NIIPPU <sup>d</sup>	PMR	Not used
Say et al. (2021)	46	ADA RT 4.40 (median)		Active NIIPPAU	Corticosteroid reduction	Not used
<b>PAEDIATRIC</b>						
Randomised trials of ADA vs. PBO (N=2)						
SYCAMORE	90	ADA + MTX vs PBO + MTX R, DB 18 mths (+6 mths follow up)	Low	JIA uveitis	Time to treatment failure <sup>b</sup>	Not used
ADJUVITE	32	ADA +/- MTX vs PBO +/- MTX R, DB 2 mths (+10 mths follow up)	High	JIA/idiopathic anterior uveitis	30% reduction of inflammation on LFP	Not used
Non-randomised studies (N=5)						
Alekseeva et al. (2012)	48	ADA vs MTX vs MTX + CiA vs oral glucocorticoid Prospective 52 weeks	High <sup>a</sup>	JIA <sup>d</sup>	Remission	Not used
Biliavska et al. (2017)	339	ADA vs tocilizumab vs etanercept Prospective 3 mths		JIA <sup>d</sup>	Disease activity, safety	Not used
Gaidar et al. (2017)	39	ADA RT, NR		JIA/active	Remission	Not used
Simonini et al. (2013)	26	ADA Prospective, 1 year		JIA/active	Time to relapse	Not used
Tynjala et al. (2008)	20	ADA + MTX RT, 18.7 mths		JIA <sup>d</sup>	Disease activity	Not used

Source: Compiled during the evaluation based on Table 2-5, pp74-78; Table 3-5, pp136-137 of the submission. Eurelings 2022, pp194-197; Fabiani 2018, pp407- 411; Lee 2018, pp1672-1673; Llorenç 2019, pp814-816; Maalouf 2022, pp 173-175; Moll-Udina 2020, pp1591-1593; Park 2020, pp177-179; Vallet 2016, pp1522-1524; NCT02916017; NCT03339102; Say et al. 2021; Alekseeva 2012; Biliavska 2017; Gaidar2017; Simonini 2013; Tynjala 2008

ACC = anterior chamber cell; ADA = adalimumab; ADR = adverse drug reaction; AnDA = anti-drug antibodies; AE = adverse events; BCVA = best-corrected visual acuity; BSC = best supportive care; CiA = conventional immunosuppressive agent; CME = cystoid macular edema; CMT = central macular thickness; CRT = central retinal thickness; DB = double blinded; EQ-5D = EuroQol 5D; HADS = Hospital Anxiety and Depression Scale; ETDRS = Early Treatment of Diabetic Retinopathy Study; HR = hazard ratio; HRU = health resource utilisation; IFX = infliximab; JIA = juvenile idiopathic arthritis; LFP = laser flare photometry; logMAR = logarithm of the minimum angle of resolution; MC = multi-centre; MTX = methotrexate; NIIPPU = non-infectious intermediate, posterior and panuveitis uveitis; NIIPPAU = non-infectious intermediate, posterior, panuveitis and anterior uveitis; NIU = non-infectious uveitis; NR = not reported; OCT = optical coherence tomography; OL = open label; PMR = post market review; R = randomised; RT = retrospective; RV = retinal vasculitis; SC = single centre; VA = visual acuity; VFQ-25 = Visual Functioning Questionnaire-25; VH = vitreous haziness; WPAI-SHP = Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire

a VISUAL III, was a single arm, open-label study and assessed for bias by the Risk Of Bias. In Non-randomised Studies - of Interventions (ROBINS)-I tool. The observational studies risk of bias (ROB) was high. The ROBINS-I moderate, serious and critical ROB is equivalent to high ROB2.

b Using a composite of 4 components: inflammatory, chorioretinal and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity

c Maalouf 2022 study was conducted in sight-threatening NIU (i.e., RV and/or CME), which was assumed to be 'active' disease. Anterior disease was not included in the description although was included in univariate analysis of factors associated with complete response and relapse.

d Controlled/active disease was not reported.

e Defined as the absence of active inflammatory lesions and AC cell grade  $\leq 0.5+$  and VH grade  $\leq 0.5+$  with concomitant steroid use or in a steroid-free state.

Blue shading indicates data previously seen by the PBAC including interim analysis of VISUAL III.

- 6.10 In the VISUAL I and II trials, patients underwent forced rapid tapering of OCS regardless of clinical response, which is not representative of clinical practice. The PBAC previously considered that the forced corticosteroid taper schedules may have overestimated the treatment effect of adalimumab (para. 7.5, ADA, PSD, March 2017 PBAC meeting). Only a proportion of patients (approximately 31% in VISUAL I and 47% in VISUAL II) were taking immunomodulatory therapy at baseline. Based on these reasons, the PBAC previously noted that that intention to treat (ITT) populations in the VISUAL I and VISUAL II trials were not representative of the eligible population under the requested listing (paras. 6.11 & 6.12, adalimumab, PSD, March 2017 PBAC meeting). The VISUAL III study and observational studies did not include forced rapid tapering of OCS and allowed the concomitant usage of both OCS and immunomodulatory therapies, which is likely to be representative of real-world practice. However, these studies were prone to a high risk of bias given their non-randomised study designs. In the VISUAL III study, the number of patients decreased significantly after week 78 because sites closed on regulatory or reimbursement approval. At week 150, only around 50% of the patients remained in the study. Further, the efficacy of adalimumab cannot be assessed in the absence of a control group.
- 6.11 The primary efficacy outcome in the VISUAL I and II trials was the time to treatment failure (i.e. flare). This was a composite outcome consisting of 4 component endpoints:
- new inflammatory, chorioretinal and/or inflammatory retinal vascular lesions relative to baseline;
  - two-step increase in anterior chamber cell grade relative to best state achieved (Standardisation of Uveitis Nomenclature; Jabs et al. 2005);

- two-step increase in vitreous haze grade relative to best state achieved (Standardisation of Uveitis Nomenclature; Jabs et al. 2005); and
- worsening of best corrected visual acuity by  $\geq 15$  letters relative to baseline (Early Treatment Diabetic Retinopathy Study chart).

6.12 The clinical trials supporting the clinical claim of superiority were unchanged since the March 2017 submission.

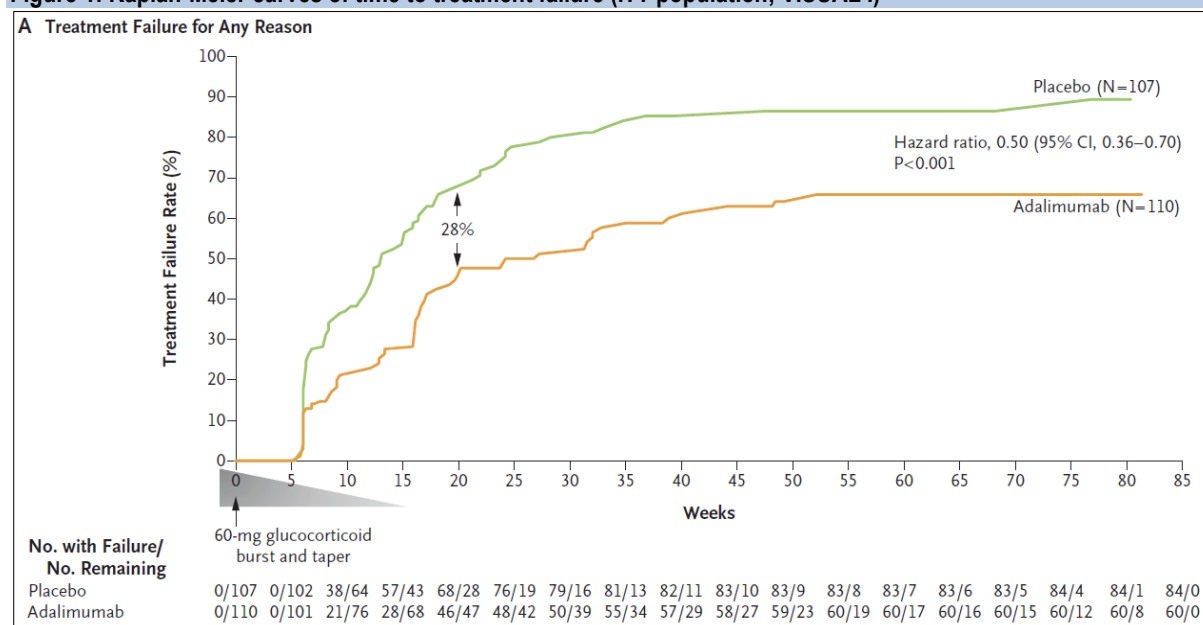
### Comparative effectiveness

#### Whole trial analysis

##### Adults

6.13 Time to treatment failure (primary outcome) with adalimumab and placebo from the VISUAL I trial is summarised in Figure 1.

**Figure 1: Kaplan-Meier curves of time to treatment failure (ITT population; VISUAL I)**



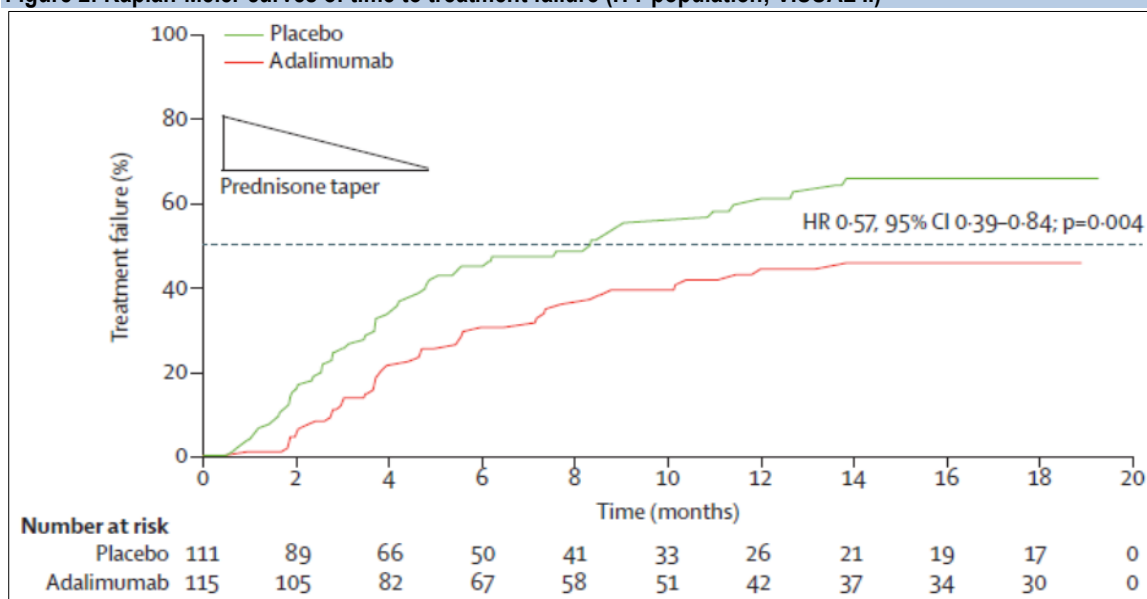
Source: Figure 1, p.938 Jaffe et al. (2016).

CI = Confidence interval; N = number; ITT = Intention to treat.

6.14 Treatment with adalimumab was associated with a statistically significant increase in time to treatment failure compared with placebo (median time to treatment failure 5.6 months vs. 3 months with placebo; hazard ratio (HR) 0.50, 95% CI: 0.36, 0.70). This was unchanged from the March 2017 submission.

6.15 Time to treatment failure (primary outcome) with adalimumab and placebo from VISUAL II is summarised in Figure 2.

**Figure 2: Kaplan-Meier curves of time to treatment failure (ITT population; VISUAL II)**



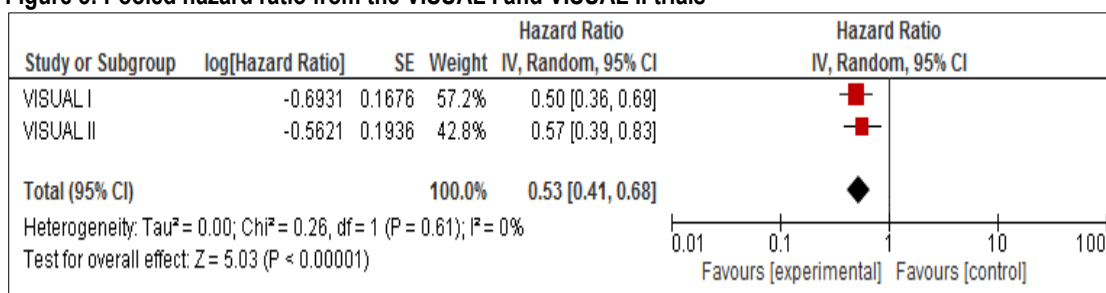
Source: Figure 2, p.1188 of Nguyen et al. (2016).

HR = Hazard ratio; ITT = Intention to treat.

6.16 Treatment with adalimumab was associated with a statistically significant increase in time to treatment failure compared with placebo (median time to treatment failure not reached vs. 8.3 months with placebo; HR 0.57, 95% CI: 0.39, 0.84). This was unchanged from the March 2017 submission.

6.17 The economic model in this resubmission used a pooled hazard ratio (HR=0.53) based on the VISUAL I and VISUAL II trials to reflect the effectiveness of adalimumab treatment compared to BSC (see Figure 3). The economic model for the original submission used the VISUAL I hazard ratio.

**Figure 3: Pooled hazard ratio from the VISUAL I and VISUAL II trials**



Source: Figure 3-11, p156 of the resubmission

CI = Confidence interval; df = Degrees of freedom; IV = Interval variable; SE = Standard error

6.18 Table 5 presents results for the primary outcome based on the VISUAL III study, i.e. the proportion of patients in quiescence defined as the absence of active inflammatory lesions and anterior chamber (AC) cell grade ≤0.5+ and VH grade ≤0.5+ with concomitant steroid use or in a steroid-free state.

**Table 5: Number and proportion of patients in quiescence (regardless of concomitant steroid use / steroid-free) (As Observed; ITT Set, VISUAL III study)**

Visit, Week	Quiescence regardless of concomitant steroid use			Steroid-free quiescence		
	Active Uveitis N = 240 n/N (%)	Controlled Uveitis N = 124 n/N (%)	Total N = 364 n/N (%)	Active Uveitis N = 240 n/N (%)	Controlled Uveitis N = 124 n/N (%)	Total N = 364 n/N (%)
0 <sup>a</sup>	18/240 (7.5) <sup>a</sup>	104/124 (83.9)	122/364 (33.5)	12/240 (5.0)	99/124 (79.8)	111/364 (30.5)
78	143/172 (83.1)	91/99 (91.9)	234/271 (86.3)	79/173 (45.7)	78/99 (78.8)	157/272 (57.7)
102	129/156 (82.7)	85/89 (95.5)	214/245 (87.3)	87/156 (55.8)	74/89 (83.1)	161/245 (65.7)
126	115/140 (82.1)	75/75 (100)	190/215 (88.4)	75/140 (53.6)	67/75 (89.3)	142/215 (66.9)
150	98/123 (79.7)	55/57 (96.5)	153/180 (85.0)	66/123 (53.7)	51/57 (89.5)	117/180 (65.0)
174	91/108 (84.3)	33/34 (97.1)	124/142 (87.3)	63/108 (58.3)	30/34 (88.2)	93/142 (65.5)
198	77/87 (88.5)	24/26 (92.3)	101/113 (89.4)	51/87 (58.6)	22/26 (84.6)	73/113 (64.6)
222	53/58 (91.4)	12/12 (100)	65/70 (92.9)	39/59 (66.1)	10/12 (83.3)	49/71 (69.0)
246 <sup>b</sup>	33/35 (94.3)	7/7 (100)	40/42 (95.2)	28/35 (80.0)	7/7 (100)	35/42 (83.3)

Source: Tables 2-26-2-27, pp111-112 of the resubmission

ITT = Intention to treat; N = Number

<sup>a</sup> Patients with active uveitis at study entry could have been in quiescence at Week 0 because all patients were evaluated for uveitis status at the Final/Early Termination visit of the lead-in study, and the Week 0 visit in the current study could have occurred up to 28 days later, during which time the patient's disease status may have changed.

<sup>b</sup> Less than 10% of patients in the ITT set at visits beyond this week (through Week 366).

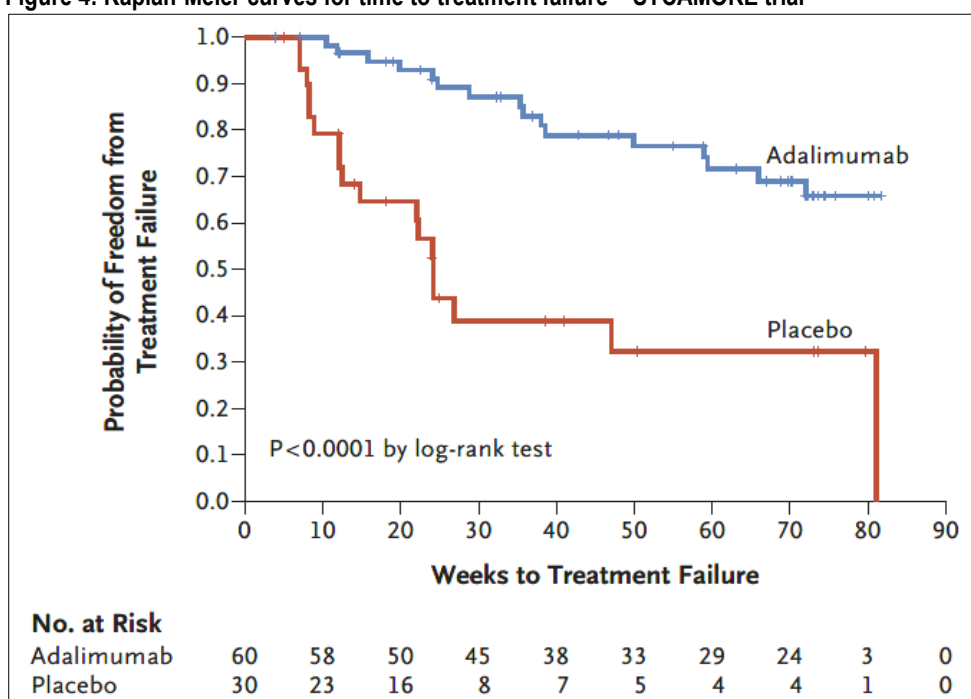
- 6.19 In the VISUAL III study, the overall proportion of patients who were in quiescence regardless of concomitant corticosteroid use increased from 33.5% (122/364) at Week 0 to 85.0% (153/180) at Week 150, with an increase in patients with active uveitis at study entry (7.5% [18/240] to 79.7% [98/123]) and with maintenance in patients with controlled uveitis (83.9% [104/124] to 96.5% [55/57]). Further, the overall proportion of patients in steroid-free quiescence in VISUAL III increased from 30.5% (111/364) at Week 0 to 65.0% (117/180) at Week 150, with an increase in patients with active uveitis at study entry (5.0% [12/240] to 53.7% [66/123]) and with maintenance in patients with controlled uveitis (79.8% [99/124] to 89.5% [51/57]). The evaluation considered that the effect of adalimumab over corticosteroids remains unclear due to the lack of data relating to the proportion of patients achieving quiescence with corticosteroids alone. Significant loss to follow-up during the study, particularly in later weeks, further complicate outcome interpretation. The high proportion of steroid-free quiescence between weeks 222 and 246 (69–83%) could have been inflated by participants not achieving quiescence dropping out of the VISUAL III study.
- 6.20 The secondary outcomes for the VISUAL I and VISUAL II trials presented in the resubmission were unchanged from the March 2017 submission.
- 6.21 In the VISUAL III study, all secondary outcomes (i.e., the mean changes in anterior chamber cell grade, vitreous haze grade, and visual acuity (i.e. logarithm of the minimum angle of resolution for the best-corrected visual acuity (log(MAR) BCVA)) mean of both eyes) from baseline to the Week 150 visit showed no meaningful difference in patients with active or controlled uveitis.

Paediatric

6.22 The SYCAMORE trial reported 16 treatment failures in 60 patients (27%) in the adalimumab arm versus 18 treatment failures in 30 patients (60%) in the placebo arm. The risk of treatment failure or uveitic flare for patients in the adalimumab arm was reduced by 75% compared to patients in the placebo arm (HR= 0.25; 95% CI 0.12–0.49; p<0.0001). Post-hoc analyses showed significant differences with a favourable response to adalimumab for both the time to treatment response (HR=3.15; 95% CI 1.42, 7.00; p<0.0027) and the proportion of responders at 3 and 6 months (p = 0.0014 for each timepoint) (Ramanan et al., 2017)<sup>7</sup>.

6.23 Figure 4 presents the Kaplan-Meier curves for time to treatment failure based on the SYCAMORE trial.

Figure 4: Kaplan-Meier curves for time to treatment failure – SYCAMORE trial



Source: Figure 2-10, p113 of the resubmission

Note: tick marks indicate censored data.

6.24 The primary efficacy endpoint in the ADJUVITE trial was the response to 2 months of treatment, expressed in terms of reducing ocular inflammation. Analysis using the ITT set showed that at month 2, there were 56.25% responders (n= 9/16) in the

<sup>7</sup> Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, Hardwick B, Hickey H, Hughes D, Woo P, and Benton D, 2017. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *New England Journal of Medicine*. 2017;376(17):1637-1646.

adalimumab arm and 20% responders (n= 3/15) in the placebo arm (relative risk = 2.81; 95% CI: 0.94, 8.45; p-value based on  $\chi^2= 0.038$ ) (Quartier et al., 2017)<sup>8</sup>.

6.25 Post hoc analyses based on the SYCAMORE trial are presented in Table 6.

**Table 6: Efficacy results for secondary outcomes and posthoc analyses based on the SYCAMORE trial, ITT set**

Outcome	ADA (N=60)	PBO (N=30)
Compliance, n (%)	NR (81.01%) <sup>b</sup>	NR (74.61%) <sup>b</sup>
Systemic corticosteroids, median duration	18 weeks (n=5)	5.6 weeks (n=1)
Topical corticosteroids reduction to <2 drops, n= 63 ≥2 drops of topical corticosteroids at randomisation, n (%)	22 (49%)	3 (17%)
Control, remission, and duration of controlled disease (uveitis)		
Mean duration of sustained controlled disease, days	179.28	14.5
Proportion of patients achieving disease control (6 months with topical treatment), n (%)	15 (25%)	1 (3%)
Proportion of patients achieving disease remission (6 months without topical treatment), n (%)	13 (22%)	0 (0%)
Health-related quality of life (CHAQ and CHQ)	No significant difference	
Time to treatment response <sup>a</sup>	HR 3.15 (95% CI: 1.42, 7.00)	
Responders by 3 and 6 months <sup>a</sup>	p=0.004 and p=0.004	
Treatment responders, n (%) <sup>b</sup>	34 (57%)	5 (17%)

Source: Compiled during the evaluation based on Table S8, Ramanan et al. (2017).

ADA = Adalimumab; CI = confidence interval; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Childhood Health Questionnaire; HR = Hazard ratio; ITT = Intention to treat; logMAR = logarithm of the minimum angle of resolution; N = Number; NR = Not reported; PBO = Placebo.

<sup>a</sup> Post-hoc analyses carried out, not pre-specified secondary outcomes.

<sup>b</sup> On average treatment compliance rates for the adalimumab arm in the double-blind and open label phases were 81.01% and 93.91% respectively, according to the patient diaries and accountability logs, and 74.61% and 83.40% for the placebo arm. Four (6%) patients in the adalimumab arm and one (3%) in the placebo arm failed treatment due to missing more than the required number of doses whilst on treatment.

### Subgroup analysis

6.26 The resubmission did not present subgroup analyses. However, the March 2017 submission presented subgroup analyses of the VISUAL I and VISUAL II trials for the primary outcome by baseline immunomodulatory therapy and by anatomical location of uveitis (intermediate, posterior or panuveitis).

6.27 In VISUAL I, the difference in time to treatment failure between treatment groups was similar regardless of whether immunomodulatory therapy was used at baseline. In VISUAL II, there was a statistically significant difference in time to treatment failure between treatment groups for patients who were taking immunomodulatory therapy at baseline, however this difference was not replicated in patients who were not taking immunomodulatory therapy at baseline.

6.28 Results of a post-hoc subgroup analysis by anatomical location of uveitis for VISUAL I and VISUAL II were collated during the previous evaluation. However, as patient

<sup>8</sup> Quartier et al. (2017) reported that the confidence interval was narrower when recalculated with a more “appropriate method for small samples” (using Koopman asymptotic score) [relative risk=2.81, 95% CI: 1.05, 8.50].

numbers were very small in each subgroup, the results from this analysis were previously considered unlikely to be meaningful.

- 6.29 In the VISUAL III study, the proportions of patients in quiescence among those with vs. without immunomodulatory therapy usage at baseline were similar (83.1% vs. 86.0% at week 150, respectively) (pp2256, 2263 of the VISUAL III study CSR). However, both VISUAL I and VISUAL II trials (as well as the VISUAL III study) were not designed, powered, or analysed to detect a difference in treatment effect based on prior immunomodulatory therapy or anatomical location of uveitis.

### Quality of life assessment

- 6.30 Table 7 presents the EuroQol 5-dimension (EQ-5D) results based on the VISUAL I and VISUAL II trials. This was unchanged from the March 2017 submission.

**Table 7: Quality of life (EQ-5D) from best state achieved prior to week 6 (VISUAL I) or baseline (VISUAL II) to final visit in the randomised trials (LOCF)**

	VISUAL I			VISUAL II		
	Mean		Mean difference between treatments (95% CI)	Mean		Mean difference between treatments (95% CI)
	ADA (N=101 <sup>a</sup> )	PBO (N=100 <sup>a</sup> )		ADA (N=101 <sup>a</sup> )	PBO (N=100 <sup>a</sup> )	
Baseline EQ-5D predicted value	0.83		NR	0.85		NR
EQ-5D predicted value	-0.04	-0.07	<b>0.04 (0.00, 0.07), p= 0.044<sup>c</sup></b>	-0.01	-0.01	0.00 (-0.03, 0.04) p= 0.836 <sup>d</sup>
EQ-5D visual analogue scale	-4.01	-7.27	3.26 (-0.72, 7.24), p= 0.108 <sup>c</sup>	-0.23	-0.13	-0.10 (-3.69, 3.48), p=0.956 <sup>d</sup>

Source: Table 11, Attachment 2.20 of the resubmission, Table B.6-10, p.99 of the March 2017 submission; p582, VISUAL I trial CSR; p481, VISUAL II trial CSR

ADA = Adalimumab; CI = Confidence Interval; CSR = Clinical Study Report; EQ-5D = European Quality of Life 5 Dimensions; LOCF = Last Observation Carried Forward; NR = Not reported; PBO = Placebo.

Bold indicates statistically significant results at 95% CI level.

Blue shading indicates data previously seen by the PBAC.

- 6.31 The change in EQ-5D scores from baseline either favoured adalimumab or were not statistically significant in the trials (VISUAL I: 0.04, p= 0.04, VISUAL II: 0.00, p= 0.836). In the long-term VISUAL III study, there was no statistically significant difference in EQ-5D scores from baseline to Week 150 (active uveitis: 0.01, 95% CI: -0.01, 0.03; controlled uveitis: 0.01, 95% CI: -0.02, 0.04).
- 6.32 The resubmission did not present health-related quality of life measures for the paediatric patients. Based on the post hoc analysis of the SYCAMORE trial data, the mean differences in Childhood Health Assessment Questionnaire (CHAQ) and Childhood Health Questionnaire (CHQ) measures were not statistically significant (Ramanan et al. 2017).

### Comparative harms

- 6.33 The resubmission noted that 398 patients (94%; 396 events/100 patient-years) experienced one or more treatment-emergent adverse events (TEAEs) in the VISUAL III study. Of these patients, 226 (53%; 80 events/100 patient-years) experienced one or more TEAEs that the investigator considered to be possibly or

- probably related to the study drug. This was consistent with the percentages reported in the VISUAL I (40.5%) and VISUAL II trials (55.7%) (VISUAL I trial CSR; p360, VISUAL II trial CSR).
- 6.34 The resubmission noted that most TEAEs (78%) in the VISUAL III study were mild or moderate in severity. Four patients reported a severe TEAE of blindness, and all were determined by the investigator to be not related to adalimumab and related to uveitis or long-term complications of uveitis. Severe or serious adverse events were experienced by 24% and 20% of patients, respectively. The percentages for severe and serious adverse events in the VISUAL III study were higher compared to those in the VISUAL I (12.6% and 13.5%, respectively) and VISUAL II trials (6.1% and 9.6%, respectively) (VISUAL I trial CSR; p360, VISUAL II trial CSR).
- 6.35 A meta-analysis of the VISUAL I and VISUAL II studies conducted during the evaluation using a random effects model found no difference in TEAEs relating to ocular disorders or complications between adalimumab and placebo (pooled relative risk 1.00, 95% CI: 0.79, 1.27).
- 6.36 In the VISUAL III study, 18.2% of patients discontinued adalimumab due to an adverse event. The percentage of patients discontinuing adalimumab was higher in the VISUAL III study compared to the VISUAL I and VISUAL II trials, where discontinuation due to TEAEs in the adalimumab arm was around 9%.
- 6.37 In the VISUAL III study, the most common TEAEs (>10%) in patients receiving adalimumab were uveitis, nasopharyngitis, arthralgia, headache, urinary tract infection, and cystoid macular oedema.
- 6.38 The most prevalent TEAEs of special interest in the VISUAL III study were infections (65%), injection site reactions (12%), and allergic reactions (7%).
- 6.39 The resubmission stated that 6 patients (1.4%; 0.5 event/100 patient-year (PY)) in the VISUAL III study reported treatment-emergent demyelinating events, including demyelination (n=2), multiple sclerosis (n=2), and optic neuritis (n=2); 5 of these patients discontinued adalimumab. The draft TGA PI for the paediatric population noted that “there is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis before initiating Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders” (TGA PI). A similar concern was raised for adult uveitis patients in the March 2017 submission (para. 6.21, adalimumab, PSD, March 2017 PBAC meeting).
- 6.40 In the SYCAMORE trial, a greater percentage of paediatric patients experienced any type of adverse event in the adalimumab arm (88%) compared with the placebo arm (83%). Serious adverse events were experienced by 22% of patients in the adalimumab arm compared to 7% in the placebo arm. The resubmission reported that adverse events were consistent with the known profile for adalimumab. However, further information relating to the safety profile of adalimumab in the trial was not presented

in the resubmission. Li et al. (2021) reported that the most common serious adverse events in the SYCAMORE trial were glaucoma, cataracts, injection site reactions, arthritis, and arthralgia. The resubmission noted that in the ADJUVITE trial, no serious adverse events were reported in the adalimumab arm during the double-blind phase. However, the long-term safety of adalimumab among the paediatric population was uncertain. The cohort size and duration of follow-up in the included trials may not be sufficient to detect changes in the rates of important adverse events associated with adalimumab.

## Benefits/harms

6.41 A summary of the comparative benefits and harms for adalimumab versus placebo is presented in Table 8.

**Table 8: Summary of comparative benefits and harms for adalimumab and placebo**

Benefits	ADA	PBO	Absolute Difference	HR (95% CI)	RR (95% CI)
<b>Trials</b>					
<b>VISUAL I (duration of follow-up: Until Week 80 or treatment failure)</b>					
Treatment failure, n/N (%)	60/110 (54.5%)	84/107 (78.5%)	2.6 months	<b>0.50 (0.36, 0.70)</b>	NA
Median time to treatment failure, months	5.6	3.0			
<b>VISUAL II (duration of follow-up: Until Week 80 or treatment failure)</b>					
Treatment failure, n/N (%)	45/115 (39.1%)	61/111 (55.0%)	-	<b>0.57 (0.39, 0.84)</b>	NA
Median time to treatment failure, months	NE	8.3			
<b>Pooled results from VISUAL I and VISUAL II</b>					
Treatment failure	105/225 (46.67%)	145/218 (66.51%)	-	<b>0.53 (0.41, 0.68)</b>	
<b>Harms</b>	<b>ADA n/N</b>	<b>PBO n/N</b>	<b>Event rate per 100 patient years<sup>a</sup></b>		
			<b>Adalimumab</b>	<b>Placebo</b>	
Any infection	112/226	82/226	145.3	139.6	<b>1.37 (1.10, 1.70)</b>
Tuberculosis	4/226	1/226	3.2	0.9	4.00 (0.45, 35.51)
Malignancies	2/226	0/226	1.9	0	5.00 (0.24, 103.57)

Source: Compiled during the evaluation based on Table B.6-1, p.89; Table B.6-11 of the March 2017 submission; Tables 2-26-2-27, 2-37 pp111-112, 127-128 of the resubmission; Figure 3-11, p156 of the resubmission; Table 14.3\_\_1.2.M VISUAL I CSR; Table 14.3\_\_1.2.M VISUAL II CSR

ADA = adalimumab; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; N = number; NA = not applicable; NE = not estimable; OLE = open label extension; PBO = placebo; RR = relative risk; TEAE = treatment-emergent adverse events

<sup>a</sup> In the VISUAL I trial, the median duration of treatment was 19 weeks for adalimumab patients and 13 weeks for placebo patients. In VISUAL II, the median duration of treatment was 35 weeks for adalimumab patients and 22 weeks for placebo patients.

Bold indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC including interim analysis of VISUAL III of OLE M11-327.

6.42 On the basis of the direct evidence from the VISUAL I trial, treatment with adalimumab, compared with placebo, resulted in a median of 2.6 months longer time to treatment failure (worsening of inflammatory markers in the eye or of visual acuity) for patients with active inflammatory disease at baseline.

- 6.43 On the basis of the direct evidence from the VISUAL II trial treatment with adalimumab, compared with placebo, resulted in a statistically significantly longer time to treatment failure (worsening of inflammatory markers in the eye or of visual acuity) for patients with controlled disease requiring relatively high doses of OCS to maintain remission.
- 6.44 On the basis of the direct evidence from the VISUAL I and VISUAL II trials presented in the submission, for patients treated with adalimumab compared with placebo there would be:
- Approximately 5.7 additional infections for 100 patients treated over a year.
  - Approximately 2.3 additional cases of tuberculosis, for 100 patients treated over a year.
  - Approximately 1.9 additional malignancies, for 100 patients treated over a year.
- 6.45 These outcomes were unchanged from the March 2017 submission.

### ***Clinical claim***

- 6.46 The resubmission described adalimumab as superior in terms of comparative efficacy over BSC and comparable in terms of safety. The March 2017 submission made the same claims.
- 6.47 The PBAC previously questioned the clinical relevance between the four composite endpoints used to define the primary efficacy outcome of time to treatment failure (flare), and the rate of downstream ocular complications such as cataracts, visual disturbance, glaucoma or blindness. The PBAC previously noted that the components of the composite measure are normally used in clinical practice to assess ocular inflammation. However, the extrapolation of the relationship between flare and ocular complication was likely to be overestimated, strongly favouring adalimumab (para. 7.8, adalimumab, PSD, March 2017 PBAC meeting). The resubmission did not present clinical evidence directly linking adalimumab treatment with ocular complications. A meta-analysis of the VISUAL I and VISUAL II trials conducted during the evaluation found no statistical difference in the incidence of ocular disorders or complications. Further, clinical evidence demonstrating a link between flares and downstream ocular complications was not presented.
- 6.48 The PSCR argued the results of the VISUAL I and II trials demonstrated the effectiveness of adalimumab at reducing the risk of recurrence or worsening of visual acuity, and VISUAL III and additional single arm observational studies showed clinically meaningful improvements or preservation of vision. Furthermore, the Response stated it received clinical advice stating it is generally accepted by the clinical community that the preservation of vision in uveitis patients correlates with the avoidance or decreased severity of other ocular complications associated with vision loss. The PSCR also argued that demonstrating a direct reduction of these complications in randomised clinical trials is often unfeasible because uveitis is

uncommon and ocular complication events are relatively rare, but can have catastrophic consequences; therefore, it is necessary to use surrogate outcomes such as flare to predict the impact of adalimumab on the prevention of ocular complications. The ESC accepted that whilst it has not been directly demonstrated, it is biologically and clinically plausible that there is a link between flares and longer-term ocular damage, and noted the effectiveness of adalimumab appears to have been accepted in practice given its use via the existing compassionate access program. However, the ESC also considered that relationship was difficult to quantify, creating uncertainty for the economic model.

- 6.49 The PBAC previously considered that the forced corticosteroid taper schedules in the VISUAL I and II trials may have overestimated the treatment effect of adalimumab (para. 7.5, ADA, PSD, March 2017 PBAC meeting). The evaluation considered this issue is unable to be resolved due to the design of the trials and remains a major source of uncertainty for assessing the magnitude of benefit of adalimumab. The PSCR argued that long term high dose corticosteroids are a clinically unacceptable treatment, contrary to treatment goals, and are only used as a last resort. The PSCR stated that from a clinical perspective, it would likely be considered unethical to maintain a patient on high dose steroids alone given the evidence demonstrating the effectiveness of adalimumab as a steroid-sparing agent, limiting the generation of any future comparative evidence. The PSCR asserted that VISUAL III, despite the absence of a control arm, allowed oral corticosteroid use and provided further evidence that adalimumab is effective with or without high dose oral corticosteroids. The ESC agreed with the evaluation and considered the design of the trials precluded a direct assessment of the comparative effectiveness of adalimumab and the comparator and was a significant source of uncertainty.
- 6.50 There was a high risk of bias in the VISUAL III study and observational studies given their non-randomised designs, which were primarily used to support long-term efficacy and safety claims. In the VISUAL III study, the number of patients decreased significantly after week 78 because sites closed on regulatory or reimbursement approval. At week 150, only approximately 50% of the patients remained in the study. Further, in the absence of a control group and in the context of using other immunomodulators, drug efficacy cannot be determined in comparison with patients who were not treated with adalimumab.
- 6.51 The evaluation considered that the long-term impact of adalimumab on flares, and subsequently ocular complications and thus the quality of life of patients with uveitis (both active and controlled) remained uncertain. The change in EQ-5D scores from baseline either favoured adalimumab or were not statistically significant in the trials (VISUAL I: 0.04,  $p=0.04$ , VISUAL II: 0.00,  $p=0.836$ , VISUAL III: active uveitis: 0.01, 95% CI: -0.01, 0.03; controlled uveitis: 0.01, 95% CI: -0.02, 0.04).
- 6.52 The ESC recalled that the PBAC previously “noted only a proportion of patients in VISUAL I and VISUAL II were taking immunomodulating therapy at baseline (approximately 31% and 47%, respectively), and there was no evaluation of treatment

effect modification by use of immunomodulatory agents” (para. 7.6, ADA, PSD, March 2017 PBAC meeting). The ESC considered the impact of immunomodulatory therapy on the efficacy of adalimumab was uncertain, and considered that this remained a matter of concern, noting that the clinical criteria of the restriction requires uncontrolled disease despite use of immunotherapy. The Pre-PBAC Response stated a subgroup analysis stratified by baseline immunomodulator therapy for the primary outcome in VISUAL II demonstrated no difference in efficacy based on this variable, suggesting immunomodulators are not a treatment effect modifier.

- 6.53 The results from the VISUAL I and VISUAL II trials demonstrated that adalimumab had an inferior safety profile to placebo. In the VISUAL I (adalimumab: 12.6% vs. placebo: 8.0%) and VISUAL II (adalimumab: 9.6% vs. placebo: 7.9%) trials a higher proportion of patients treated with adalimumab experienced severe adverse events. As noted by the previous evaluation, the adverse event profile of adalimumab, including infections, tuberculosis, cancer and multiple sclerosis, is different to the adverse event profile of OCS, which include heart disease, osteoporosis, diabetes, and cataracts (para. 6.27, adalimumab, PSD, March 2017 PBAC meeting). The ESC considered the evidence suggested adalimumab has an inferior safety profile to BSC, however acknowledged long-term use of corticosteroids is associated with known significant morbidities that were not captured in the clinical trials. The Pre-PBAC Response argued Australian real-world data provided through the consumer comments support a conclusion that adalimumab is a highly effective and steroid-sparing treatment and that the comments articulated the impacts and side effects of long-term, high dose corticosteroids.
- 6.54 The submission also claimed superior efficacy and comparable safety in the paediatric population. While the presented evidence suggested potential benefits of treatment with adalimumab for paediatric non-infectious uveitis, both the SYCAMORE and ADJUVITE trials had several limitations. These limitations included: small sample sizes (SYCAMORE: 90 patients, ADJUVITE: 32 patients), early termination of the SYCAMORE trial, a potential high risk of bias in the ADJUVITE trial, and the inclusion of JIA-associated uveitis only in the SYCAMORE trial. Furthermore, female representation was disproportionately high in both trials (SYCAMORE: 78% and ADJUVITE: 94% in the adalimumab arm), as such their broad applicability to the Australian population is uncertain. A detailed discussion of the trial characteristics is presented in the ‘Clinical trials and studies’ section above.
- 6.55 The PBAC considered that the magnitude of benefit of adalimumab over BSC in terms of uveitis flares was difficult to quantify due to the design of the pivotal trials which precluded a comparison with OCS, and that the benefit in terms of ocular complications could not be directly assessed due to the lack of long term comparative data. However, the Committee considered the claim of superior efficacy of adalimumab over placebo was supported.
- 6.56 The PBAC agreed with the ESC and considered the available evidence suggested adalimumab has an inferior safety profile to BSC, but that a comparison to long-term

use of corticosteroids was not possible and acknowledged the known morbidities of long-term OCS could not be captured in the comparison.

### **Economic analysis**

6.57 The resubmission presented a stepped economic evaluation comparing ADA ± OCS vs. BSC ± OCS based on the pooled results of the VISUAL I and VISUAL II trials. The type of economic evaluation presented was a cost-utility analysis (CUA). This approach remained unchanged from the March 2017 submission.

6.58 An economic evaluation for the paediatric population was not presented. The PSCR argued that given there are limited clinical trial and epidemiological data on the paediatric population, the economic evaluation is based on the adult population; however also argued that if adalimumab is shown to be acceptably cost effective in the adult population, it would likely be equally or more cost effective in the paediatric population, where the consequences of irreversible ocular complications will accrue a greater disease burden and quality of life implications are experienced over a lifetime.

6.59 Table 9 presents the key components of the economic model.

**Table 9: Summary of model structure, key inputs and rationale in the resubmission**

<b>Component</b>	<b>March 2017 submission</b>	<b>Resubmission</b>
Target PBS population	Vision threatening NIIPPU	Vision threatening non-infectious uveitis.  The resubmission removed the reference to specific anatomic locations from the proposed patient population definition. The applicability of the economic model results to patients with anterior disease was unclear.
Model population	Entry age: 43 years, 57% female (based on VISUAL I)	No change. Reducing the mean age to 36.6 years based on Australian observational studies (Lee et al. (2018); Say et al. (2021)) had a minimal impact on the ICER.
Treatments	ADA ± OCS vs. BSC ± OCS. Both treatment arms received OCS tapered over 4 months. Patients who experienced a flare (acute ocular complications) also received OCS.	No change.  Tapering of OCS in clinical practice may take longer than 4 months depending on the treatment response (Airody et al. 2015 and Foster et al. 2016). The PBAC previously noted that “corticosteroid tapering will vary depending on clinician preference as well as disease severity and response, and in severe cases patients have at least two to three courses of corticosteroid treatment per year” (para. 7.5, ADA, PSD, March 2017 PBAC meeting).
Outcomes	Proportion of patients free of ocular complications, QALYs.	Proportion of patients free of flare / failure, life years gained, QALYs.
Methods used to generate results	Markov cohort analysis, 1-month cycles; half cycle correction.	No change
Time horizon	Lifetime (up to 57 years, maximum age 100 years) in the model base case vs. up to 80 weeks in the VISUAL I trial (median duration of treatment 13 weeks for	No change. The submission explored the impact of a time horizon of 10 and 20 years in one-way SA (Table 14).

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Component	March 2017 submission	Resubmission	
	placebo; 19 weeks for ADA).		
Health states	State-transition model with 19 health states: 8 treatment states, 1 disease remission state, 6 acute ocular complications states, 3 chronic ocular complications states and dead.	State-transition model with 20 health states: same 18 health states but 2 health states for disease resolution (pre-incident flare, post-incident flare; previously called disease remission).	
Transition probabilities			
Probability of ocular complications, BSC arm	Monthly probabilities calculated based on 5-year probabilities from Dick et al. (2016).	Applied Dick et al. (2016) but 'adjusted' by subtracting the risks of ocular complications in the control group without uveitis.	The ESC considered this was appropriate and addressed previous concerns (para. 6.40, and Table 7, ADA, PSD, March 2017 PBAC meeting).  The ICER increased from \$25,000 to < \$35,000 to \$35,000 to < \$45,000/QALY gained after correcting the monthly probability of glaucoma in the model to align with the per cycle probability calculated in the submission (Table 3-6 of the submission).  The PSCR accepted this correction to the economic model and the updated base case ICER.
	Monthly probabilities for acute ocular complications: Cataract 0.0138 Retinal detachment 0.0023 Visual disturbance 0.0089	Monthly probabilities for acute ocular complications: Cataract 0.0114 Retinal detachment 0.0021 Visual disturbance 0.0073	
	Monthly probabilities for chronic ocular complications: Glaucoma 0.0061 Retinal disorder 0.0090 Blindness 0.0006	Monthly probabilities for chronic ocular complications: Glaucoma 0.0044 (model applied 0.0073) Retinal disorder 0.0086 Blindness 0.0004	
Probability of ocular complications, ADA arm	HR 0.50 (95% CI 0.36-0.70) (risk of inflammatory flare, VISUAL I); assumed an implicit 1:1 relationship between the reduction in flares and the reduction in the risk of ocular complications; applied for the duration of the model.	HR 0.53 (pooled VISUAL I and VISUAL II trials). <sup>a</sup> No tapering of efficacy over time.  Base case: continued to assume a 1:1 relationship between the reduction in flares and the reduction in the risk of ocular complications.	
Probability of disease resolution	Assumed 63.3% of patients experienced disease resolution after 5 years of ADA treatment (Dick et al. 2016).	0.51%/cycle based on treatment discontinuation rate due to remission from Eurelings 2022 for the first 5 years, assumed 100% disease resolution after a maximum of 5 years without flare; same for both treatment arms.	
ADA treatment discontinuation	Assumed on ADA treatment for 5 years in the pre-incident state; after 5 years, 63.3% (Dick et al. 2016) experienced disease resolution and the remaining 36.7% continued ADA for another 5 years if	Model structure amended to model treatment discontinuation due to remission (0.51%/cycle) or due to other reasons (0.84%/cycle) based on Eurelings et al. (2022).	

Component	March 2017 submission	Resubmission
	not having a flare. After that, assumed all patients experienced disease resolution.	
	Assumed patients in remission/resolution did not require ADA or BSC treatment.	No change.
Utilities	Baseline 0.85 (source not reported), remission 0.85 (assumed same as baseline).  QALY loss for flare from VISUAL I utility and wait time for elective surgery.  Literature-based utilities from various sources for ocular complications.  Applied disutility for OCS but not to ADA treatment.	No change except: (a) no longer applied a disutility to OCS treatment; and (b) estimated the QALY loss associated with cataract using updated data. <sup>c</sup>
Costs	Unit costs from literature, MBS/PBS	Source of unit costs broadly similar, updated to the recent schedules and inflated to 2023 dollars.  The drug cost (DPMQ \$████) for adalimumab applied in the economic model differed from the DPMQ requested in Table 1-7, p45 of the resubmission.  The cost of immunomodulators was not included in the model.

Source: Tables 3-1, 3-8 to 3-10, 3-12, 3-15 and 3-17 and Figure 3-11, pp39-40, 45-48, 156, 166-170, 173 and 177 of the resubmission; Table 6, para. 2.3,2.4, 2.4, 6.2, 6.5 and 7.3, pp1-2, adalimumab, PSD, March 2017 PBAC meeting; Tables A.1-1, D.4-5 to D.4-8, pp32 and 173-176 of the March 2017 submission

ADA = adalimumab; AEMP = Approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; BSC = best supportive care; CI = Confidence Interval; DPMQ = Dispensed Price for Maximum Quantity; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; NIIPPU = non-infectious intermediate, posterior or panuveitis; OCS = oral corticosteroid; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; QALY = Quality-adjusted life year; SA = sensitivity analysis; SD = Standard deviation; TGA = Therapeutic Goods Administration; vs. = versus.

Blue shading indicates data previously seen by the PBAC.

a The resubmission presented a Forest Plot figure (Figure 3-11, p156 of the resubmission) to show the results of the pooling, using a random effects (inverse variance) model in synthesis.

b The resubmission reported that Leal et al. (2022) was a retrospective review of 51 patients with non-infectious uveitis (102 affected eyes) in the UK and the study supported that a link coefficient of at least 0.85 was justifiable (Table ES.4, p22 of the resubmission).

c Weighted average based on 98 days and 7 days of wait-time for elective surgeries in public (60%) and private (40%) hospitals (AIHW 2019-20). The March 2017 submission estimated the weighted average based on 83 days and 7 days of wait-time for elective surgeries in public (60%) and private (40%) hospitals (AIHW 2014-15).

6.60 When compared with the economic evaluation in the March 2017 submission, the resubmission:

- Addressed previous concerns, including: (i) overestimating the treatment effect of adalimumab on the risk of ocular complications due to the use of an ‘unadjusted’ background risk of ocular complications, (ii) use of the HR from the VISUAL I trial only, and (iii) the application of disutilities for AEs associated with OCS but not for AEs associated adalimumab;

- Made slight modifications to the model structure: (i) 2 health states for disease remission were added; and (ii) patients could discontinue treatment due to remission or due to other reasons; and
  - Updated selected input parameters with more recent data, including: Eurelings et al. (2022) and PBS list price.
- 6.61 The resubmission, however, did not provide clinical evidence supporting the direct link between adalimumab treatment and ocular complications, or sequentially link active flares to ocular complications in the economic model. The resubmission continued to model the incidence of ocular complications over a lifetime horizon and apply the treatment effect of adalimumab on the risk of flares to the risk of ocular complications. The resubmission continued to assume a 1:1 relationship (“link coefficient”) between a reduction in the risk of flares and a reduction in the risk of ocular complications. The incremental cost-effectiveness ratio (ICER) remained highly sensitive to the time horizon and the treatment effect of adalimumab on the risk of ocular complications (Table 14).
- 6.62 The March 2017 submission used (a) Dick et al. (2016)<sup>9</sup> to inform the probabilities of various ocular complications in the BSC arm and (b) estimated the probabilities of ocular complications in the adalimumab arm by applying a reduced risk of inflammatory flare (HR 0.50, 95% CI 0.36, 0.70) from the VISUAL I trial to the background probabilities in the BSC arm (which the PBAC considered overestimated the treatment effect of adalimumab). The resubmission therefore used a pooled<sup>10</sup> estimate (HR 0.53, 95% CI 0.41, 0.68) from both VISUAL I and II trials. The ESC considered this was reasonable, however noted the 95% CI were wide. Using the upper 95% CI of the pooled HR (0.68) increased the ICER from \$25,000 to < \$35,000 to \$75,000 to < \$95,000 per quality-adjusted life year (QALY) gained.
- 6.63 Based on issues raised by the previous evaluation regarding the use of unadjusted probabilities (see Table 14), the resubmission ‘adjusted’ the probabilities by subtracting the probabilities in the control group without uveitis. The evaluation considered that this was reasonable.
- 6.64 The March 2017 submission implicitly assumed a 1:1 relationship between the reduction in flares and the reduction in the risk of ocular complications. The PBAC previously noted that although “almost all” patients with non-infectious intermediate, posterior or panuveitis (NIIPPU) will experience flare, “only a proportion of patients will go on to experience long-term complications” and therefore by “not including the occurrence of uveitic flares over time in the model the uncertainty of the relationship

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<sup>9</sup> A large retrospective analysis of US insurance claims data, which estimated the time to first ocular complication in patients with posterior, intermediate or panuveitis and matched controls.

<sup>10</sup> The resubmission presented a Forest Plot figure (Figure 3-11, p156 of the resubmission) to show the results of the pooling but did not provide details on the method used. Labels in the figure appeared to indicate that the resubmission employed a random effects inverse variance model in synthesis.

between flare and ocular complications was increased” (para. 7.13, adalimumab, PSD, March 2017 PBAC meeting). The resubmission argued that there was no evidence in the clinical trial data suggesting an adalimumab flare is more severe than a placebo flare and continued to assume a 1:1 relationship between the reduction in flares/treatment failure and the reduction in the risk of ocular complications. The resubmission made the 1:1 relationship explicit by introducing a “link coefficient,” set in the base case as one. The resubmission reported that the link coefficient was used to “capture the proportion of ocular complications avoided relative to the number of flares avoided as measured in the clinical trial”. The resubmission explored the impact of a link coefficient of 0.85 in a sensitivity analysis (Table 14). This was based on Leal et al. (2022),<sup>11</sup> who retrospectively reviewed 51 patients with non-infectious uveitis (102 affected eyes) in the UK. The study found that 13 out of 51 patients (20 eyes; unilateral in 6 patients) experienced treatment failure after 12 months, after starting adalimumab (the resubmission). Of the 20 eyes that experienced treatment failure, 17 (85%) eyes experienced failure because of worsening visual acuity (7 eyes due to macular oedema, 4 eyes due to cataract development, 6 eyes due to unspecified and miscellaneous reasons such as advanced glaucoma, corneal decompensation, etc.). The resubmission did not provide clinical evidence directly linking adalimumab treatment with ocular complications. Lowering the link coefficient to 0.85 increased the ICER to \$45,000 to < \$55,000/QALY gained (Table 14).

- 6.65 The PSCR argued that using a link coefficient of less than one biases against adalimumab. The Response argued, using the sensitivity analysis link coefficient of 0.85 applied in the evaluation, that such an approach increases the HR for flares with ocular complications, and given the pooled HR from VISUAL I/II applies to flares overall that this would imply a reduction in the HR for flares that do not lead to ocular complications. For the sensitivity analysis link coefficient of 0.85, the Response stated this would imply a HR for non-ocular complicating flares of 0.13, which is unrealistic as that means a flare in the adalimumab arm is 13% more likely to result in ocular complications than a flare in the comparator arm. Furthermore, the Response argued the data from the VISUAL trials indicate the proportion of patients experiencing treatment failure due to worsening visual acuity (as a proxy for events leading to ocular complications) was slightly lower in the adalimumab arm than the comparator arm (31.4% vs 34.5%, respectively), further supporting the case for a link coefficient of 1 in the base case analysis. The ESC agreed with the evaluation and considered the link coefficient relationship of 1:1 likely overestimated the adalimumab treatment effect due to the inherent uncertainty of downstream events and therefore agreed a lower coefficient would be more clinically plausible. The Pre-PBAC Response acknowledged a lower link coefficient is more conservative but argued it is not more clinically plausible to assume an adalimumab flare is more severe and more likely to

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<sup>11</sup> Leal I, Wong SW, Giuffre C, Patil A, Sousa DC, Barbosa-Breda J, Chhabra R, Jones NP, & Steeples LR. Real-World outcomes of adalimumab in adults with non-infectious uveitis. *Acta Ophthalmologica* 2022;100(7):e1496-e1502.

result in complications when compared to BSC, which would be the net effect of lowering the coefficient. The Response also reiterated that treatment failure in the VISUAL trials due to worsening visual acuity was slightly lower in the adalimumab arm than the BSC arm (31.4% vs 34.5%, respectively).

- 6.66 The lifetime time horizon was another key issue raised by the PBAC regarding the March 2017 submission. The time horizon in the model (lifetime: entry age 43 years, model duration 57 years) was long compared to the maximum duration of follow-up in the trials (VISUAL I and VISUAL II: 80 weeks) and the open-label extension study (VISUAL III study<sup>12</sup>). The PBAC previously considered “As there was considerable uncertainty between flares and ocular complications, the PBAC did not consider the lifetime time horizon appropriate and that it significantly overestimated the cost effectiveness of adalimumab. The PBAC suggested important differences in costs and outcomes would be captured in a 10 year time horizon given majority of ocular complications are expected to occur within 2–5 years” (para. 7.14, adalimumab, PSD, March 2017 PBAC meeting). The resubmission did not make any changes to the time horizon but explored the impact of a time horizon of 10 and 20 years in one-way sensitivity analyses. The evaluation considered that a shorter time horizon may better reflect the treatment of a single episode of non-infectious uveitis, however, it would potentially underestimate the longer-term QALY impact of ocular complications resulting in permanent vision loss. The ICER remained sensitive to the time horizon. Decreasing the model duration from a lifetime (57 years) to 10 and 5 years increased the ICER to \$115,000 to < \$135,000 and \$255,000 to < \$355,000 /QALY gained, respectively (Table 14).
- 6.67 The PSCR argued the use of a lifetime time horizon was reasonable and consistent with the PBAC Guidelines, given the goal of treatment in uveitis patients is to avoid permanent vision loss and other irreversible ocular complications, and a shorter time horizon would undervalue the impact of permanent ocular complications and permanent vision loss as the impacts are lifelong. The ESC noted the model is highly sensitive to the time horizon, and agreed in principle the effects of permanent vision loss have significant impacts on quality of life over a person's lifetime. However, the ESC also considered that given the uncertainty of the magnitude of relationship between the surrogate outcome (flares) and modelled ocular complication, that it may be reasonable to explore a shorter time horizon to reduce uncertainty; but acknowledged a shorter time horizon would exclude plausible ongoing quality of life benefits associated with avoiding ocular complications. The Pre-PBAC Response agreed with the ESC view that a shorter time horizon would exclude plausible ongoing benefits, and argued it is not appropriate or necessary to apply an arbitrary reduction

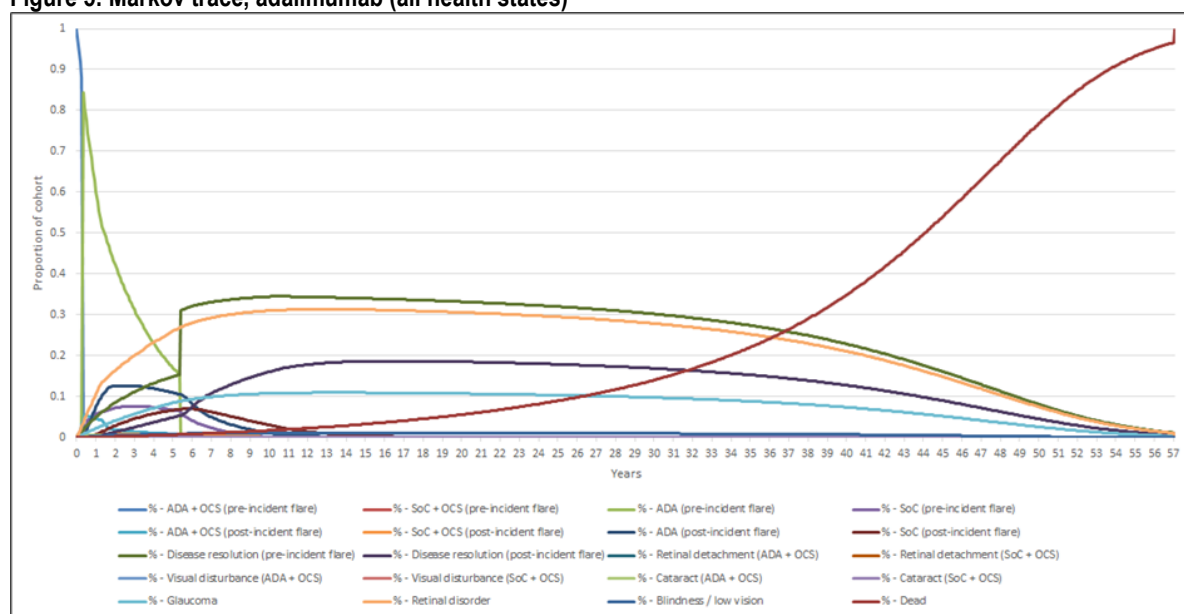
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<sup>12</sup> The VISUAL III study was originally planned for 78 weeks but extended to week 366. At Week 78, Around 75% and 50% of the patients were retained at week 78 and week 150, respectively. By week 246, less than 10% were retained. No results are reported beyond Week 246.

in time horizon; rather, the Response argued the model includes a link coefficient variable to allow exploration of potential uncertainty of the surrogate outcome (flares) and modelled ocular complications.

6.68 Figure 5 and Figure 6 present the Markov traces for adalimumab ( $\pm$  OCS) and BSC ( $\pm$  OCS) over time, respectively.

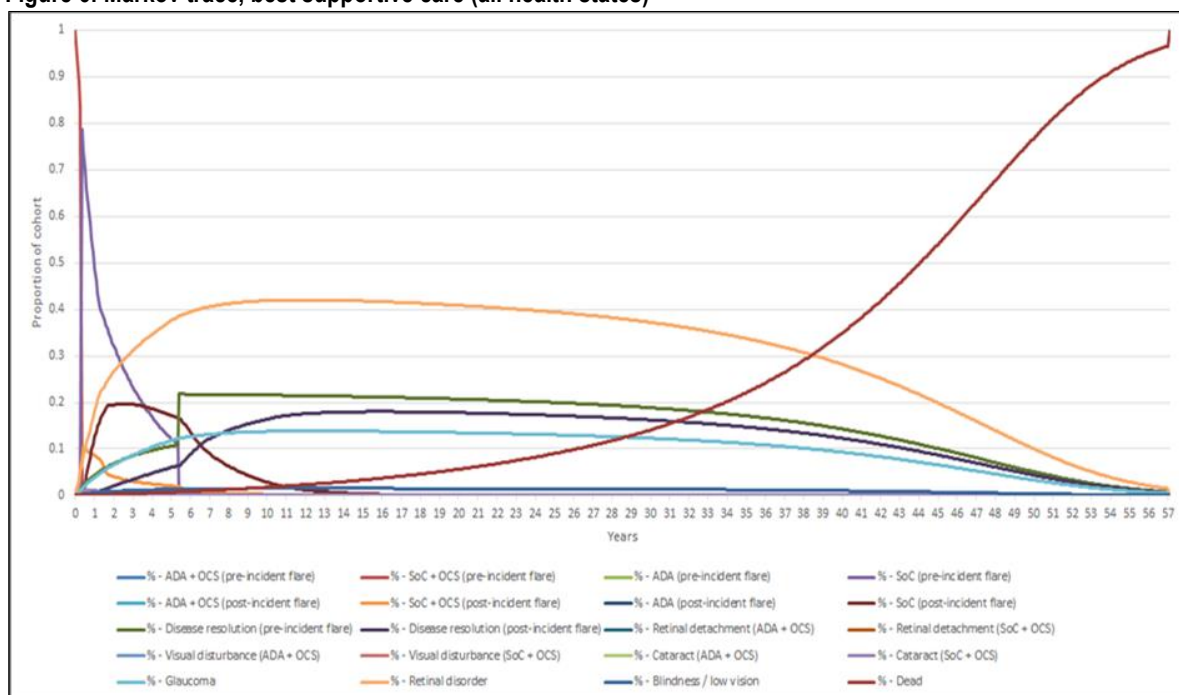
Figure 5: Markov trace, adalimumab (all health states)



Source: Figure 3-12, p181 of the resubmission.

ADA = adalimumab; OCS = oral corticosteroid; SoC = standard of care/best supportive care.

Figure 6: Markov trace, best supportive care (all health states)



Source: Figure 3-13, p182 of the resubmission.

ADA = adalimumab; OCS = oral corticosteroid; SoC = standard of care/best supportive care.

6.69 The March 2017 submission assumed 63.3% of patients experienced disease resolution after 5 years of adalimumab (based on Dick et al. 2016).<sup>13</sup> The current resubmission assumed disease resolution for all patients in both treatment arms without flare after a maximum of 5 years. Consequently, the relative proportion of patients entering remission at 5 years was higher in the adalimumab treatment arm, reflecting a greater share of patients remaining free of ocular complications over this period (see Figure 5 and Figure 6). The resubmission reported that assuming a maximum disease duration of 5 years (i.e., time without flares before remission was induced) did not infer a maximum treatment duration of 5-years overall, as a share of the adalimumab cohort remained on treatment beyond 10 years due to the recency of incident ocular complications. The ESC agreed with the evaluation and considered this was highly uncertain and noted non-infectious uveitis may reoccur, necessitating retreatment. Eurelings et al. (2022)<sup>14</sup> reported the uveitis recurrence-free survival interval to be 3.4 years (range, 0-13 years). Assuming no maximum disease duration increased the ICER from \$25,000 to < \$35,000 to \$55,000 to < \$75,000 /QALY gained (Table 14).

<sup>13</sup> Dick AD, Tundia N, Sorg R, Zhao C, Chao J, Joshi A & Skup M. Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmology* 2016;123(3):655-662.

<sup>14</sup> Eurelings LEM, Missotten T, van Velthoven MEJ, van Daele PLA, van Laar JAM, van Hagen PM, Thiadens A & Rombach SM. Long-Term Follow-up of Patients With Uveitis Treated With Adalimumab: Response Rates and Reasons for Discontinuation of Therapy. *Am J Ophthalmol* 2022;240:194-204.

- 6.70 The March 2017 submission estimated the expected duration of adalimumab therapy based on the proportion of uveitis patients that remained at risk of ocular complications and therefore required treatment (Dick et al. 2016). The previous evaluation noted that ocular complications are potential downstream effects of uveitis and are therefore of limited relevance in determining treatment duration (para. 6.35, adalimumab, PSD, March 2017 PBAC meeting). The resubmission slightly modified the structure of the Markov model to explicitly model treatment discontinuation as health state transitions. The probability of adalimumab treatment discontinuation due to controlled disease (0.51%/cycle) or due to other reasons (0.84%/cycle) was applied based on Eurelings et al. (2022). The PSCR reiterated the probability of disease resolution was based on evidence from Eurelings et al. (2022), which included adalimumab treatment discontinuation rates due to remission, and further argued the assumptions used in the model remain consistent with Dick et al. 2016 which was relied upon in the 2017 submission. The ESC considered the assumptions around disease resolution were not well supported by the available evidence. The Pre-PBAC Response reiterated the disease resolution rate applied in the model reflects that observed in empirical evidence from 342 patients treated with adalimumab (16.7% over 3.2 years from Eurelings et al), and the application of these data to the model is further supported by the comparable disease resolution rate in 112 Australian patients provided by the Royal Victorian Eye and Ear Hospital (RVEEH) in their organisational consumer comments (¶ III)<sup>15</sup>. The PBAC considered that while the disease resolution rates were based on empirical evidence, it was overall acceptable to apply these to the economic model.
- 6.71 The utility inputs in the resubmission model remained largely unchanged. A key difference was the removal of the disutility associated with OCS treatment, for “consistency and simplicity”. The March 2017 submission applied disutility from OCS treatment but not from adalimumab treatment, which the PBAC previously considered to be inappropriate (para. 7.15, adalimumab, PSD, March 2017 PBAC meeting). In response, the resubmission did not apply a disutility to either adalimumab or OCS treatment. The resubmission argued that “given the worse safety profile of OCS compared to adalimumab, the exclusion of QALY impacts of OCS related adverse events is unambiguously biased against adalimumab”. No direct evidence of the comparative safety of adalimumab and OCS was provided to support this assumption. In the VISUAL I trial, there was a statistically significant difference between treatment arms in favour of adalimumab for the change in EQ-5D scores (p=0.04). In the VISUAL II trial, there was no statistically significant difference between treatment arms for change in EQ-5D scores. The EQ-5D scores would have captured the impact of any differences in adverse events between adalimumab and OCS on utilities in the short term, however any differences may have been underestimated in

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<sup>15</sup> Note that the data provided by the Royal Victorian Eye and Ear Hospital (RVEEH) is part of a manuscript which is currently under preparation, to be submitted in 2025. This information will be unredacted at such time that the paper is published.

the long term due to forced tapering of OCS in the trials. The effect of re-including disutilities associated with OCS adverse events on the ICER was minimal.

6.72 The resubmission made the following changes to costs compared with the March 2017 submission: adalimumab price reduction, accounting for monthly instead of 4-weekly cycles (both adalimumab and OCS), updating the cost of OCS based on the current PBS DPMQ for prednisolone, updating the costs of ocular complications, including the cost of AEs with adalimumab treatment and updating the cost of AEs with OCS treatment.

6.73 Table 10 presents the disaggregated costs per person by treatment arm.

**Table 10: Health care resource items: disaggregated summary of cost impacts**

Resource item	ADA (± OCS)		BSC (± OCS)		Increment	
	Cost	% of total	Cost	% of total	Cost	% of total cost-offsets
<b>Pharmaceutical products</b>						
ADA treatment	\$	29.9	\$0	0.0	\$	
OCS treatment	\$	0.2	\$154.87	0.3	-\$	0.2
Total	\$	30.1	\$154.87	0.3	\$	
<b>Management of AEs</b>						
ADA AEs	\$	0.2	\$0	0.0	\$	
OCS AEs	\$	5.2	\$4,009.55	6.5	-\$	3.3
Total	\$	5.4	\$4,009.55	6.5	-\$	2.4
<b>Acute ocular complications</b>						
Retinal detachment	\$	0.5	\$444.89	0.7	-\$	0.7
Visual disturbance	\$	0.0	\$18.09	0.0	-\$	0.0
Cataract	\$	1.4	\$1,280.00	2.1	-\$	2.1
Total	\$	2.0	\$1,742.97	2.8	-\$	2.9
<b>Chronic ocular complications</b>						
Glaucoma	\$	35.0	\$31,243.82	50.7	-\$	53.0
Retinal disorder	\$	26.1	\$23,224.72	37.7	-\$	39.3
Blindness	\$	15.0	\$1,303.44	2.1	-\$	2.2
Total	\$	62.5	\$55,771.98	90.4	-\$	94.4
<b>Overall total</b>	\$		<b>\$61,679.37</b>	<b>100</b>	<b>\$</b>	<b>-\$ (100%)</b>

Source: Table 3-20, p187 of the resubmission

ADA = adalimumab; AE = adverse event; BSC = best supportive care; OCS = oral corticosteroid.

6.74 The cost of adalimumab treatment (\$ ) was offset significantly by the cost savings from the modelled reduction in chronic ocular complications (-\$), resulting in an overall incremental cost of \$.

6.75 Table 11 presents the disaggregated health outcomes by treatment arm.

**Table 11: Disaggregated summary of health outcomes included in the economic evaluation**

Outcome	Outcome for ADA ± OCS	Outcome for BSC ± OCS	Incremental outcome	NNT
LYs (undiscounted)	41.6859	41.6859	0.0000	
LYs (discounted)	17.2881	17.2881	0.0000	
QALYs (discounted)	13.9602	13.7333	0.2268	
ADA treatment duration	3.1410	0	3.1410	
OCS treatment duration	0.5387	0.6089	-0.0702	
<b>Acute ocular complications, average number of events per patient over a lifetime time horizon</b>				
Retinal detachment	0.0404	0.0465	-0.0061	165
Visual disturbance	0.1232	0.1616	-0.0383	26
Cataract	0.2201	0.2523	-0.0322	31
<b>Chronic ocular complications, average number of events per patient over a lifetime time horizon</b>				
Glaucoma	0.2369	0.2991	-0.0623	16
Retinal disorder	0.2791	0.3524	-0.0733	14
Blindness	0.0130	0.0164	-0.0034	291

Source: Table 3-21, p188 of the resubmission.

ADA = adalimumab; BSC = best supportive care; LY = life year; NNT = number needed to treat; OCS = oral corticosteroid; QALY = quality-adjusted life year.

6.76 There was no change in life years gained between treatment groups, and so the QALYs gained were due to improvements in quality of life. The resubmission did not report QALYs disaggregated by health state.

6.77 Table 12 presents the key model drivers of the model.

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

Description	Method/Value	Impact Base case: █/QALY gained
Time horizon	Lifetime (model duration 57 years based on entry age of 43 years and up to a maximum of 100 years of age).	High. A longer model duration favours adalimumab. Using a 10-year time horizon, that was previously suggested by the PBAC, increased the ICER to █ <sup>2</sup> /QALY gained.
Treatment effect of adalimumab on the risk of ocular complications	Risk of flares (HR= 0.53, 95% CI 0.41-0.68), pooled estimate taken from the VISUAL I and II trials and applied a 1:1 relationship (linkage coefficient 1) to the risk of ocular complication in model.	High. A greater reduction in risk of flares for adalimumab and/or assuming a stronger linking relationship between risk of flares and ocular complications favours adalimumab. <ul style="list-style-type: none"> <li>Using the upper bound of the 95% CI of the pooled HR increased the ICER to █<sup>3</sup>/QALY gained.</li> <li>Lowering the linkage coefficient to 0.85 increased the ICER to █<sup>4</sup>/QALY gained.</li> </ul>
Maximum disease duration	Five years	Moderate. A shorter disease duration favours adalimumab (earlier transitioning to remission state, avoiding ocular complications). Assuming no maximum duration increased the ICER to █ <sup>5</sup> /QALY gained.

Source: p189 of the resubmission.

CI = Confidence Interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

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

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$45,000 to < \$55,000

<sup>5</sup> \$55,000 to < \$75,000

6.78 Table 13 presents the results of the stepped economic evaluation in the resubmission.

**Table 13: Results of the stepped economic evaluation in the resubmission**

Step and component	ADA (± OCS)	BSC (± OCS)	Increment
<b>Step 1a: Trial-based costs and outcomes (VISUAL I) (time horizon 12 months)</b>			
Costs (ADA/OCS costs only)	\$ <sup>a</sup>	\$	\$
Patient free of flare / failure	0.344	0.138	0.206
Incremental cost/extra patient free of flare / failure			\$ <sup>1</sup>
<b>Step 1b: Trial-based costs and outcomes (VISUAL II) (time horizon 12 months)</b>			
Costs (ADA/OCS costs only)	\$	\$	\$
Patient free of flare / failure	0.559	0.397	0.162
Incremental cost/extra patient free of flare / failure			\$ <sup>2</sup>
<b>Step 2a: Modelled analysis (time horizon 12 months)</b>			
Costs (ADA/OCS costs only)	\$	\$	\$
Patient free of flare / failure	0.772	0.612	0.160
Incremental cost/extra patient free of flare / failure			\$ <sup>2</sup>
<b>Step 2b: Modelled analysis (time horizon 12 months)</b>			
Costs (ADA/OCS costs only)	\$	\$	\$
Flare / failure avoided	0.241	0.430	0.189
Incremental cost/extra flare / failure avoided			\$ <sup>1</sup>
<b>Step 3: Transform to QALYs (time horizon 12 months)</b>			
Costs (ADA/OCS costs only)	\$	\$	\$
QALYs	0.8848	0.8756	0.0092
Incremental cost/extra QALY gained			\$ <sup>3</sup>
<b>Step 4: Introduce cost of flares (time horizon 12 months)</b>			
Costs (ADA/OCS, OC costs)	\$	\$	\$
QALYs	0.8848	0.8756	0.0092
Incremental cost/extra QALY gained			\$ <sup>3</sup>
<b>Step 5: Introduce AE impacts for ADA and OCS (time horizon 12 months)</b>			
Costs (ADA/OCS, OC, AE costs)	\$	\$	\$
QALYs	0.8848	0.8756	0.0092
Incremental cost/extra QALY gained			\$ <sup>3</sup>
<b>Step 6: Extrapolate to lifetime horizon</b>			
Costs (ADA/OCS, OC, AE costs)	\$	\$	\$
QALYs	13.6340	13.4026	0.2314
Incremental cost/extra QALY gained			\$ <sup>4</sup>
<b>Step 7: Introduce ADA discontinuations</b>			
Costs (ADA/OCS, OC, AE costs)	\$	\$	\$
QALYs	13.5443	13.4026	0.1416
Incremental cost/extra QALY gained			\$ <sup>4</sup>
<b>Step 8: Introduce disease remission per cycle</b>			
Costs (ADA/OCS, OC, AE costs)	\$	\$	\$
QALYs	13.8336	13.6504	0.183
Incremental cost/extra QALY gained			\$ <sup>5</sup>
<b>Step 9: Introduce maximum disease duration of 5 years</b>			
Costs (ADA/OCS, OC, AE costs)	\$	\$	\$
QALYs	13.9602	13.7333	0.2268
Incremental cost/extra QALY gained (base case)			\$ <sup>6</sup>
<b>Previous consideration (March 2017 PBAC meeting)</b>			
Costs	\$	\$	\$
QALYs	13.401	13.031	0.370
Incremental cost/extra QALY gained (base case)			\$ <sup>2</sup>

Source: Tables 3-19 and 3-22, pp186 and 188 of the resubmission; Excel workbook titled

“StepEconEval\_extrairformation\_Abbvie\_ADA\_Uveitis” supplied upon request during the evaluation.

ADA = adalimumab; AE = adverse event; BSC = best supportive care; OC = ocular complication; OCS = oral corticosteroid; QALY = quality-adjusted life year.

<sup>a</sup> \$ [redacted] = (\$ [redacted] / 2) \* 28

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$755,000 to < \$855,000

<sup>4</sup> \$135,000 to < \$155,000

<sup>5</sup> \$55,000 to < \$75,000

6.79 The resubmission reported that over the lifetime horizon, adalimumab was associated with an incremental cost of \$ [redacted] per patient, and 0.2268 QALYs. The ICER was \$25,000 to < \$35,000 per QALY gained.

6.80 The resubmission (vs. March 2017 submission) reported that for every 1,000 patients modelled to be treated with adalimumab, there will be:

- 3 (vs. 9) fewer patients with blindness as a complication.
- 32 (vs. 203) cataract procedures avoided.
- 62 (vs. 91) fewer patients developing glaucoma.
- 38 (vs. 132) fewer patients experiencing a visual disturbance.
- 73 (vs. 133) fewer patients developing a retinal disorder.
- 6 (vs. 34) fewer patients experiencing a retinal detachment.

6.81 The evaluation considered these results should be interpreted with caution:

- Correcting the monthly probability of glaucoma in the BSC +/- OCS arm to 0.0044 increased the ICER to \$35,000 to < \$45,000/QALY gained.
- The resubmission did not provide clinical evidence directly linking adalimumab treatment with ocular complications.
- The resubmission assumed that the disease resolves after 5 years.
- The proposed DPMQ for adalimumab was \$706.70 for 2 x 20 mg and \$676.79 for adalimumab 2 x 40 mg or 1 x 80 mg. However, the economic evaluation results were based on an assumed DPMQ of \$ [redacted] for 2 x 40 mg, which the resubmission calculated based on a proposed flat ex-manufacturer price of \$ [redacted] per script for the 20 mg, 40 mg and 80 mg strengths, plus an assumed [redacted] % future price reduction from price disclosure and a lower wholesale margin of \$ [redacted] for the 40 mg and 80 mg scripts. The price disclosure-related assumptions were speculative at time of submission and price reductions through this policy cannot be prospectively determined. The PSCR stated the indicative April 2024 price disclosure cycle had determined an adalimumab AEMP (for the relevant dose form) of \$505.95. At time of ESC advice, the Department advised these prices had not been finalised; however, they were finalised prior to consideration by the PBAC, with an AEMP of \$505.95 for the 2 x 40 mg form confirmed.

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

**Table 14: Results of key univariate and multivariate sensitivity analyses**

	Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
	<b>Base case (BC)</b>	\$	0.2268	1	-
<b>Univariate sensitivity analyses</b>					
A	Probability of glaucoma = 0.0044 (base case 0.0073) <sup>a</sup>	\$	0.2174	2	%
<b>Time horizon (BC = 57 years)</b>					
B	20 years	\$	0.1650	3	%
C	10 years <sup>b</sup>	\$	0.1032	4	%
	5 years	\$	0.0554	5	%
<b>Adalimumab efficacy (BC = 0.53)</b>					
D	Upper 95% CI of HR of pooled VISUAL I/II (0.68) <sup>c</sup>	\$	0.1350	6	%
	Lower 95% CI of HR of pooled VISUAL I/II (0.41) <sup>c</sup>	\$	0.3109	7	%
<b>Link co-efficient (BC = 1:1 relationship between the reduction in the time to treatment failure and the reduction in the risk of ocular complications)</b>					
E	Link co-efficient 1:0.85 <sup>d</sup>	\$	0.1819	8	%
	Link co-efficient 1:0.75 <sup>d</sup>	\$	0.1537	3	%
	Link co-efficient 1:0.5 <sup>d</sup>	\$	0.0890	9	%
<b>Maximum disease duration (BC = 5 years)</b>					
F	No maximum (99 years) <sup>e</sup>	\$	0.1831	3	%
	10 years <sup>e</sup>	\$	0.1903	3	%
	3 years <sup>e</sup>	\$	0.2393	7	%
<b>Discount rate (BC = 5% per annum)</b>					
	0%	-\$	0.5493	Dominant	-
	3.5%	\$	0.2831	7	%
<b>Adalimumab DPMQ (BC = \$)</b>					
G	\$676.79 (requested DPMQ)	\$	0.2268	8	%
H	\$579.19 (\$505.95 AEMP) <sup>f</sup>	\$	0.2268	1	%
<b>Multivariate sensitivity analyses (exploratory)</b>					
	A and C	\$	0.0963	10	%
	A and D	\$	0.1306	11	%
	A and E	\$	0.1753	3	%
	A, C and E	\$	0.0793	10	%
<b>ESC requested</b>					
	A, C, D, E, and F	\$	0.0509	12	%
	A, C, E, F, and H	\$	0.0784	10	%
<b>PBAC requested</b>					
	A and H	\$	0.2174	2	%
	A, E and H	\$	0.1753	3	%
	A, E, H and B	\$	0.1273	11	%
	A, E, H and C	\$	0.0793	10	%

Source: Table 3-23, pp191-193 of the resubmission.

BC = base case; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

<sup>a</sup> The resubmission stated that it applied 0.0044 for the monthly probability for glaucoma, however 0.0073 was applied in the economic model. In the resubmission's TreeAge model, changed variable the value of p\_oc\_SoC\_glau from 0.0073 to 0.0044 (Table 3-6, p160 of the resubmission).

<sup>b</sup> Changed the value of variable duration\_yrs from 57 (base case) to 10.

<sup>c</sup> Changed the value of variable HR\_flare\_ADA from 0.53 (base case) to 0.68 or 0.41.

<sup>d</sup> Changed the value of variable HR\_link\_coeff from 1 (base case) to 0.85, 0.75 or 0.5.

<sup>e</sup> Changed the value of variable max\_disease\_dur\_yrs to 99, 10, or 3.

<sup>f</sup> DPMQ = Calculated as AEMP + wholesaler markup of \$38.05 + AHI fee of \$26.82 + Dispensing fee of \$8.37

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$255,000 to < \$355,000

<sup>6</sup> \$75,000 to < \$95,000

<sup>7</sup> \$5,000 to < \$15,000

<sup>8</sup> \$45,000 to < \$55,000

<sup>9</sup> \$135,000 to < \$155,000

<sup>10</sup> \$155,000 to < \$255,000

<sup>11</sup> \$95,000 to < \$115,000

<sup>12</sup> \$355,000 to < \$455,000

- 6.83 As in the March 2017 submission, the ICER remained sensitive to the model time horizon and to the treatment effect attributed to adalimumab on the risk of ocular complications. The ICER was also sensitive to the maximum disease duration.
- 6.84 The ESC considered additional sensitivity analyses would be useful (shown in Table 14).
- 6.85 The Pre-PBAC Response argued the patient, clinician and organisational inputs in the consumer comments highlighted that there is an inherent quality of life benefit evident for patients treated with adalimumab. The Response noted that the model does not capture quality of life benefits associated with lowered anxiety and peace of mind from being free of flare, as well as increased ability to re-engage with activities that are important to patients as a result of increased visual acuity.

### Drug cost/patient /year

6.86 Table 15 presents the drug cost per patient per year for adults and paediatrics.

Table 15: Drug cost per patient for adalimumab ± OCS

	Trial dose and duration	Model	Financial estimates
<b>Current resubmission</b>			
Mean dose	VISUAL I and VISUAL II: 80mg at week 0, 40 mg fortnightly	Loading dose 80 mg at week 0, 40 mg fortnightly	Adults: Incident, induction: 50% one 80 mg dose, 50% two 40 mg doses. Incident & grandfathered continuing: one 40 mg script/month. Paediatric, induction and continuing: 20% on 20 mg dose, 80% on 40 mg dose.
Mean duration	VISUAL I: 205.4 days (15.9 doses) <sup>c</sup> ; VISUAL II: 300.2 days (22.7 doses) <sup>c</sup>	3.14 years	Incident patients: continued ADA treatment unless discontinued (15.59% per year). Grandfathered patients: continued ADA treatment from Year 1 unless discontinued (20% per year).
DPMQ	\$676.79 [A]	\$ [A]	40 mg, 80 mg: \$ [A] 20 mg: \$ [G]
Max. quantity [B]	2 [B]	2 [B]	-

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	Trial dose and duration	Model	Financial estimates
Cost/injection [C=A/B]	\$338.40 [C=A/B]	\$ [C=A/B]	-
Injections frequency	-	1-month cycles [D] Cycle 1: 3 Cycle 2+: 2.1726 <sup>a</sup>	Adults/paediatric.: Incident patients: 13 scripts in Year 1 (one script for induction, 12 additional scripts), Year 2+: 12 scripts/year Grandfathered patients: 12 scripts/year.
Cost/patient/month		[E = C x D] Cycle 1: \$ [ ] Cycle 2+: \$ [ ]	-
Cost/patient/year (chronic)	Year 1 <sup>c</sup> : VISUAL I: \$10,760.96 [A x 15.9] VISUAL II <sup>c</sup> : \$15,363.13 [A x 22.7]  Year 2+: VISUAL I <sup>c</sup> : \$0 VISUAL II <sup>c</sup> : \$0	[F = E x 12] Year 1: \$ [ ] Year 2+: \$ [ ]	Incident, adults: Year 1: \$ [ ] [A x 13]. Year 2: \$ [ ] [A x 12]. Grandfathered continuing, adults: Year 1: \$ [ ]; Year 2: \$ [ ] [A x 12]. Incident paediatric: Year 1: \$ [ ] [(A x 80% + G x 20%) x 13] Year 2: \$ [ ] [(A x 80% + G x 20%) x 12]

Source: Table 2-15, p95 of the resubmission; pp23, 170 and 199-200 of the resubmission; Excel Workbook titled "Attachment 3.2 Humira\_Uveitis\_Section2" of the resubmission; para. 6.44 and 6.45, adalimumab, Minutes, March 2017 PBAC meeting; Table 14.1\_3.1.2.M, p549 of the VISUAL I trial CSR; Table 14.1\_3.1.2.M, p452 of the VISUAL II trial CSRADA = adalimumab; CSR = Clinical Study Report; DPMQ = Dispensed Price for Maximum Quantity; OCS = oral corticosteroid.

<sup>a</sup> The resubmission applied 2.1726 injections per cycle from cycle 2 onwards. It appeared that the resubmission calculated the injections per cycle based on 365 days rather than 365.25 a year [2.1726 = (365/12)/14]. Had the resubmission used 365.25 days a year, the number of injections per cycle from cycle 2 onwards would be 2.1741 [(365.25/12)/14], resulting in \$ [ ] per cycle from cycle 2 onwards.

<sup>b</sup> These estimates could not be reproduced. Using the same method as in the economic model which applied 3 injections (1 x 80 mg loading dose, 2 x 40 mg injections) in the first cycle and 2.1726 injections per cycle thereafter, the estimated cost of adalimumab treatment is: \$ [ ] per patient in the first year - comprising the cost of the first model cycle \$ [ ] [= \$ [ ] + (\$ [ ]/2) x 2], plus the cost of the remaining 11 cycles at \$ [ ] each cycle [= (2.1726 x \$ [ ]/2)]; and \$ [ ] per patient per year thereafter - comprising 12 one-month cycles at \$ [ ] each cycle.

<sup>c</sup> Based on the mean number of doses received over the course of treatment with adalimumab; Year 2 costs for both trials were zero due to the short treatment duration (i.e. 205.4 days in the VISUAL I trial and 300.2 days in the VISUAL II trial).

6.87 The resubmission reported that the cost of treatment in the first year was \$ [ ] (28 doses), followed by treatment costs of \$ [ ] (26 doses) per year thereafter (based on a DPMQ of \$ [ ]). The number of injections (28) in the initial year in the resubmission was slightly greater than the number of injections (27.5 = 2 + 51/2) in the March 2017 submission (para. 6.44, adalimumab, PSD, March 2017 PBAC meeting).

6.88 The resubmission's estimates could not be reproduced during the evaluation. Using the same method as in the resubmission's economic model, the estimated cost of adalimumab treatment was \$ [ ] per patient in the first year and \$ [ ] per patient per year thereafter (based on a DPMQ of \$ [ ]).

6.89 The resubmission did not present the drug cost per patient per year for the proposed paediatric population, which is likely to be different (owing to different dose regimens, as a minimum). This was calculated during the evaluation (see Table 15 above).

### Estimated PBS usage & financial implications

6.90 The Drug Utilisation Sub Committee (DUSC) considered this resubmission. In 2017, the PBAC noted the DUSC's "concerns regarding the patient numbers and re-treatment"

and “considered a risk share arrangement should include revised financial estimates and a % rebate above the agreed cap” (para. 7.17, adalimumab, PSD, March 2017 PBAC meeting). The resubmission did not request a risk-sharing agreement for the proposed listing. Adalimumab is currently in the F2 formulary and multi-branded with several biosimilars listed; therefore, a risk sharing agreement would likely not be feasible to implement.

6.91 The resubmission used data from the Australian AbbVie Compassionate Access Program (1 January 2019 - June 2023) to estimate the number of patients likely to be treated with adalimumab for non-infectious uveitis in Year 1 (2024). This was changed from the March 2017 submission, which based the population on Australian patients with uveitis (Zagora et al., 2016), the proportion with uveitis referred to specialist, the proportion of referred patients with non-infectious intermediate, posterior and panuveitis, an adalimumab uptake rate of % in Year 1 and rising to % in Year 6), < 500 grandfathered patients and a discontinuation rate of 10.93%.

6.92 Table 16 presents the key inputs for the financial estimates in the resubmission.

**Table 16: Key inputs for financial estimates in the resubmission**

Parameter	Value applied and source	Comment
Incident patients	Year 1 (2024): ■ <sup>1</sup> (■ <sup>1</sup> adults, ■ <sup>1</sup> paediatric patients), Year 6: ■ <sup>1</sup> (■ <sup>1</sup> adults, ■ <sup>1</sup> paediatric patients).  Year 1: estimated the first full year based on the number of new patients in the Australian AbbVie Compassionate Access Program in the first half of 2023 and inflated by around 20% to allow for growth and patients switching from the SAMF. Years 2-6 applied population growth to the previous year.	Uncertain and potentially underestimated. The resubmission assumed the Compassionate Access Program and the SAMF captured 100% of all the patients who would be treated under the proposed PBS listing. The resubmission assumed all those currently eligible under the Compassionate Program and the SAMF would also be treated under the proposed PBS listing. However, the alignment of the access criteria to the Compassionate Program could not be verified as the access criteria were not reported. The eligibility criteria of the SAMF were more stringent than the proposed PBS restrictions for adults.  The DUSC considered the growth rate per year was uncertain and possibly underestimated as it was substantially lower than the annual growth reported from the Compassionate Access Program. However, the growth rate in the early years of the Compassionate Access Program may have been higher than its future annual growth on the PBS, due to growing awareness of the treatment and the program.
Grandfathered patients	Year 1 (2024): ■ <sup>2</sup> (■ <sup>2</sup> adults, ■ <sup>1</sup> paediatric patients), discontinuing at a rate of 20% per annum to Year 5: ■ <sup>1</sup> (■ <sup>1</sup> adults, ■ <sup>1</sup> paediatric patients) and to none in Year 6.	The discontinuation rate is uncertain and inconsistent with the rate from Eurelings et al. 2022 used in the economic model.
Compliance rate	Assumed 100%, as non-compliance already accounted for in the annual discontinuation rate.	This was reasonable.

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Parameter	Value applied and source	Comment
Dose/duration	Adults: Loading dose – assumed 50% used 1 x 80 mg dose and 50% used 2 x 40 mg doses. After the first month, assumed one script/month.	One 40 mg script per month after the first month was a slight underestimation owing to a fortnightly injection schedule as recommended by the TGA-approved PI. It was also inconsistent with the economic evaluation (which used 2.1726 injections/cycles after the first month).
	Paediatric patients: for both induction and continuing doses, assumed 20% used 20 mg dose, 80% used 40 mg dose (Compassionate Program, usage in 2023, to end of June).	The resubmission did not consider the use of 80 mg as a loading dose for patients ≥30 kg. Financial estimates were slightly underestimated owing to a slightly greater DPMQ for 20 mg.
Discontinuation rate per year	Incident patients: 15.59% every year (Eurelings et al. (2022) (10.93% in the March 2017 submission).	This was consistent with the economic model for adults. In the paediatric SYCAMORE trial, 15% of the patients in the adalimumab arm discontinued (a total of 9 patients who discontinued (n = 60), 7 discontinued during the follow-up period, 2 refused to enter into follow-up).
	Grandfathered patients: assumed 20% every year, decreased to 0 after 5 years.	
Drug cost for adalimumab	DPMQ ██████ for 40 mg and 80 mg doses, DPMQ \$ ██████ for 20 mg dose.	The drug cost (DPMQ) for adalimumab applied in the financial model differed from the DPMQ requested in Table 1-7, p45 of the resubmission.
Offsets for comparator/ subsequent therapies	None applied.	The impact on corticosteroids and immunomodulatory agents were not included. The economic model included treatment costs for flares and ocular complications.
MBS item	None applied	Not appropriate. Underestimated financial impact. Relevant MBS items include <sup>a</sup> : 104, 105, 109.

Source: Tables 4-3 to 4-7, pp197-199 of the resubmission; pp10-11 of draft TGA PI for adalimumab.

DPMQ = Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; SAMF = South Australian Medicines Formulary.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

6.93 Table 17 presents a summary of the estimated use and financial implications in the resubmission.

Table 17: Estimated use and financial implications in the resubmission

	2024	2025	2026	2027	2028	2029
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated						
Adult patients	1	1	1	1	1	1
Paediatric patients	2	2	2	2	2	2
Total	1	1	1	1	1	1
Number of scripts dispensed <sup>a</sup>						
	3	3	3	3	3	3
<b>Estimated financial implications of adalimumab: DPMQ \$█ for 40mg, 80 mg / DPMQ \$█ for 20mg</b>						
Adult patients (\$)	4	4	4	4	4	4
Paediatric patients (\$)	4	4	4	4	4	4
Total cost to PBS/RPBS less copayments (\$)	4	4	4	4	4	4
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments (\$)	4	4	4	4	4	4
<b>Net financial implications</b>						
Net cost to PBS/RPBS (\$)	4	4	4	4	4	4
Net cost to MBS/ Services Australia/other (\$)	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS/Services Australia (\$)	4	4	4	4	4	4
<b>Updated pricing: DPMQ \$579.19 for 20 mg, 40 mg, 80 mg</b>						
Adults (\$)	4	4	4	4	4	4
Paediatrics (\$)	4	4	4	4	4	4
Total (\$)	4	4	4	4	4	4
<b>Previous submission (March 2017 PBAC meeting): revised net impact to the government (at reduced effective DPMQ and including paediatric patients)</b>						
	2017	2018	2019	2020	2021	2022
Adult patients treated per year	2	1	1	1	1	1
Cost to the Govt. (\$)	4	4	4	4	4	4
Paediatric patients treated per year	2	2	42	2	2	2
Cost to the Govt. (\$)	4	4	4	4	4	4
<b>Total (\$)</b>	4	4	4	4	5	5

Source: Tables 4-7, 4-11, 4-13 to 4-15, pp199, 201 and 203-204 of the resubmission; tab '3a. Scripts – proposed' in Excel Workbook titled 'Attachment 4.1 Utilisation and Cost Model Humira Uveitis' of the resubmission; Tables 8-9, para. 6.51, adalimumab, Minutes, March 2017 submission).

DPMQ = Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits.

<sup>a</sup> Assuming one script for each initiating patient and 12 scripts per year as estimated by the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

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

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

6.94 At year 6, the estimated number of patients treated with adalimumab was 500 to < 5,000 (500 to < 5,000 adult, < 500 paediatric). The total cost to the PBS/RPBS of listing adalimumab was estimated to be \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing (based on a DPMQ of \$█).

- 6.95 The number of incident patients was potentially underestimated because the resubmission assumed the AbbVie Compassionate Access Program and the South Australian Medicines Formulary (SAMF) captured 100% of the patients who would be treated and also the growth in patient numbers under the proposed PBS listing. The alignment of the eligibility criteria to access the Australian AbbVie Compassionate Access Program, the SAMF and the proposed PBS listing is unclear. The DUSC noted the resubmission increased the estimated number of treated patients based on the Compassionate Access Program by 20% to account for the SAMF, but considered the number of patients who have accessed adalimumab through the SAMF was unknown and it is unclear whether the indication for access to this program aligns with the requested restriction. The Pre-PBAC Response acknowledged compassionate access is not a usual source of data to inform financial estimates, however stated these data represent the real utilisation of adalimumab since the access program has existed, and the validity of these data to reflect the proposed population is supported by the widespread knowledge and uptake among the small group of clinicians who manage this condition. The Response also noted there is direct alignment of the proposed PBS restrictions with the compassionate access program and SAMF access criteria.

### **Quality Use of Medicines**

- 6.96 The resubmission reported that a risk management plan, including an Australian-specific annex had been submitted to the TGA as part of the regulatory dossier. There will also be an AbbVie Care patient support program available to provide support to prescribers and patients regarding the use of adalimumab.

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

- 6.97 The PBAC previously noted that the proposed restriction for uveitis did not exclude patients with other systemic diseases treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) and might allow less restrictive access to adalimumab than current restrictions for systemic diseases and leading to leakage. The pre-PBAC response at the time proposed a risk share agreement with subsidisation caps to manage uncertainties to ensure access to the appropriate patients” (para. 2.4, adalimumab, PSD, March 2017 PBAC meeting). The PBAC noted a Risk Sharing Arrangement would likely not be feasible for the listing of adalimumab in non-infectious uveitis as it is now multi-branded with several biosimilars listed on the PBS.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the General Schedule, Authority Required listing of adalimumab for the treatment of vision-threatening non-infectious uveitis, on the basis the listing would be acceptably cost effective at the price proposed in the pre-PBAC response. The PBAC considered the available evidence supported the effectiveness of adalimumab in reducing uveitis flares, and that whilst the magnitude

of the relationship between flares and long-term ocular damage was uncertain, accepted patients would likely experience vision-preserving benefits through improved flare control.

- 7.2 The PBAC was satisfied that adalimumab provides, for some patients, a significant improvement in efficacy over best supportive care (BSC), defined as high dose corticosteroids, with or without an immunomodulatory agent (as described in paragraph 5.1), however noted the available evidence did not allow a robust estimate of the magnitude of benefit (discussed further below). The Committee also noted treatment with adalimumab will allow some patients to cease or reduce use of concomitant corticosteroids and/or other immunomodulators which was of benefit given the known adverse events associated with prolonged use of these agents at high doses.
- 7.3 The PBAC acknowledged there was a clear unmet need and clinical place for effective treatments for non-infectious uveitis on the PBS. The PBAC noted adalimumab was available for non-infectious uveitis through a Sponsor-supported compassionate access program and a state-based access program in South Australia.
- 7.4 The PBAC welcomed consumer input from patients (many of whom use or have used adalimumab for this condition), family members, health professionals and organisations. All input strongly supported the PBS listing of adalimumab, describing the benefits of treatment as including reduced flares, reduced ocular damage and in some cases, reversal of existing damage. The PBAC noted the comments also described the benefits of being able to reduce or eliminate concomitant use of corticosteroids and avoiding associated side effects.
- 7.5 The PBAC noted additional work will be required by the Department to finalise the restriction, and considered the restriction should include the following:
- An Authority Required (written/electronic for initial therapy and telephone/electronic for continuing therapy/grandfather patients) listing. The PBAC recalled in 2017 it considered there was a risk the listing for non-infectious uveitis may allow 'less restrictive' access to adalimumab (Table 2 refers), however considered that with the biosimilar uptake drivers and changes following reviews of PBS authorities, biologic or targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) listings were already (in some cases) less restrictive than in 2017;
  - The restriction should be age-agnostic, with criteria relating to prior therapy and steroid dose requirements reflecting the differing needs of adult and paediatric patients;
  - Specific reference to anatomical location or phenotype of uveitis was not required, as whilst anterior uveitis in adult patients is often manageable with short-term steroids and/or systemic therapies, anterior uveitis is important for the paediatric population. Overall, the PBAC considered the risk of clinically

inappropriate use of adalimumab based on anatomical location of disease was low;

- No requirement for treatment withdrawal after a period of steroid-free quiescence; however, the PBAC considered a re-initiation restriction for patients who do attempt to withdraw adalimumab and experience flares may be warranted if the initial restriction is a barrier to patient needs;
- An initial treatment period of 25 weeks' (loading dose in week 1 with quantities and repeats to provide 24 additional weeks' treatment in the initial phase) with continuing treatment at intervals of 24 weeks, with appropriate quantities and repeats; and
- Prescribing to be limited to ophthalmologists, rheumatologists or immunologists with expertise in managing non-infectious uveitis, or in consultation with these prescribers.

7.6 The PBAC reaffirmed its March 2017 advice that the appropriate comparator was best supportive care defined as high-dose oral corticosteroids, with or without an immunomodulatory agent. The PBAC noted the dose of corticosteroids considered 'high' will vary between adult and paediatric patients.

7.7 The PBAC noted the randomised clinical trial evidence presented in the submission included the VISUAL I and II trials in adult patients and the SYCAMORE and ADJUVITE trials in paediatric patients. The PBAC noted the VISUAL I/II trials were previously considered in March 2017. The VISUAL I trial required patients to be in a flare state for inclusion, whereas VISUAL II required patients to have controlled disease but be on high dose corticosteroids. The PBAC noted the trials in paediatric patients had not been previously considered. The SYCAMORE trial included 90 patients aged 2–18 years with juvenile idiopathic arthritis (JIA)-associated uveitis. The trial was terminated early because efficacy was demonstrated and subsequently patients in the placebo arm crossed over to be treated with adalimumab. The ADJUVITE trial included 32 patients aged 4 years or older with idiopathic or JIA-associated uveitis. The PBAC noted an additional 19 observational studies were presented assessing longer-term efficacy and safety of adalimumab.

7.8 The PBAC noted adalimumab was associated with a statistically significant increase in time to treatment failure (i.e. flare) compared to placebo in both the VISUAL I and II trials (pooled HR for the two trials: 0.53, 95% CI 0.41, 0.68). The PBAC considered the magnitude of comparative benefit of adalimumab over corticosteroids alone was unclear as both trials included a forced corticosteroid tapering phase. Results were presented for VISUAL III, the open label extension study for VISUAL I and II, for the proportion of patients in quiescence regardless of steroid use and in quiescence without corticosteroids, however the PBAC considered the effect of adalimumab over corticosteroids remained unclear due to the lack of data on the proportion of patients achieving quiescence with corticosteroids alone. The PBAC acknowledged however, that long term high dose corticosteroids are associated with substantial morbidity and

are avoided in clinical practice.

- 7.9 Given the proposed restriction requires uncontrolled disease despite use of immunomodulatory therapy, subgroup analyses of VISUAL I and II were presented based on the use of these therapies. The PBAC noted that the use of immunomodulatory therapy did not appear to greatly impact on the efficacy of adalimumab.
- 7.10 The PBAC noted in the SYCAMORE trial adalimumab resulted in an increase in the time to treatment failure (Figure 4 refers), the mean duration of sustained controlled disease (179 vs 15 days), proportion of patients achieving disease control or remission (47% vs 3%) and proportion of treatment responders (57% vs 17%). The PBAC noted the intention-to-treat (ITT) analysis of the ADJUVITE trial showed that at month 2, 56.25% (9/16) of patients in the adalimumab arm were responding, compared to 20% (3/15) in the placebo arm.
- 7.11 Overall, the PBAC considered that the magnitude of benefit of adalimumab over BSC in terms of uveitis flares was difficult to quantify due to the design of the pivotal trials which precluded a comparison with OCS, and that the benefit in terms of ocular complications could not be directly assessed due to the lack of long term comparative data. However, the Committee considered the claim of superior efficacy of adalimumab over placebo was supported.
- 7.12 The PBAC recalled its previous view in March 2017 that adalimumab and corticosteroids have different safety profiles, and noted the key clinical evidence was largely the same in the current submission, which indicated adalimumab is likely to have an inferior safety profile to placebo. However, the Committee acknowledged that long-term use of high dose corticosteroids is associated with significant morbidity and this was not captured in the short-term comparative trials which mandated a reduction in the corticosteroid dose.
- 7.13 The PBAC noted the structure of the economic model was similar to that considered in March 2017, with some of the changes previously requested by the PBAC implemented. The key model drivers related to the efficacy of adalimumab in reducing flares and subsequently ocular complications. The PBAC noted the estimates for both of these inputs were uncertain and that the uncertainty was magnified with a longer time horizon. The ICER, after correcting the probability of glaucoma (to 0.0044 per month) and using the adalimumab price as confirmed in the pre-PBAC response (1 April 2024 AEMP \$505.95 [DPMQ \$579.19] for the 2 x 40 mg injection form), was \$35,000 to < \$45,000 per QALY gained. The PBAC noted that the updated economic and financial outcomes were based on a flat ex-manufacturer price per script for the 20 mg, 40 mg and 80 mg strengths.
- 7.14 In terms of the impact of adalimumab on flares, the PBAC noted the pooled estimate from the VISUAL I and II trials was used. As outlined in paragraph 7.11, the magnitude of benefit with adalimumab versus remaining on corticosteroids was uncertain, however the PBAC accepted that long term use of high doses of corticosteroids is

associated with significant morbidity and avoided in clinical practice, and therefore considered it reasonable for the efficacy estimates from VISUAL I and II to inform the economic model.

- 7.15 In terms of the impact of adalimumab on ocular complications, the PBAC noted it was assumed that there is a 1:1 relationship between a reduction in flares and a reduction in ocular complications. The PBAC noted there was limited clinical data to inform the relationship, however agreed with the ESC that a link between repeat flares and downstream ocular complications was biologically plausible, although difficult to quantify reliably. The PBAC noted changing the relationship to 1:0.85 increased the ICER to \$55,000 to < \$75,000 per QALY gained.
- 7.16 The PBAC acknowledged that a time horizon longer than 10 years was likely reasonable to account for plausible ongoing quality of life benefits over a person's lifetime associated with avoiding downstream ocular complications and vision-loss, however noted that the extent of reduction in ocular complications over time was uncertain. In this context, the PBAC noted that using a model time horizon of 20 years and 10 years increased the ICER to \$95,000 to < \$115,000 and \$155,000 to < \$255,000 per QALY gained, respectively.
- 7.17 Overall, in the context of the high clinical need and small patient population, the PBAC considered adalimumab was likely cost-effective at the price proposed in the pre-PBAC response.
- 7.18 The PBAC noted that the population considered in the economic evaluation was adults with uveitis, however considered the cost effectiveness of adalimumab was likely to be similar regardless of patient age.
- 7.19 The PBAC considered the existing compassionate access schemes provided a reasonable foundation for estimating the likely prevalent pool of patients that would use adalimumab when listed on the PBS. The PBAC considered the assumption of a 20% increase in patients over the number currently enrolled in the sponsor access program to account for the South Australian program and growth was reasonable, and noted that this resulted in 500 to < 5,000 adult and < 500 paediatric patients treated in the first year of PBS listing compared with 500 to < 5,000 adults and < 500 paediatric patients currently in the sponsor access program. The PBAC noted using the price proposed in the pre-PBAC response that the estimated net cost to the PBS/RPBS was \$40 million to < \$50 million over 6 years. The PBAC noted that because adalimumab is multi-branded with biosimilars, a Risk Sharing Arrangement was likely not feasible for this listing.
- 7.20 The PBAC noted multiple biosimilars were available for adalimumab and considered existing 'a' flagging arrangements should be implemented for the listing for non-infectious uveitis.
- 7.21 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 adalimumab:

- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy in terms of a reduction in uveitis flares, and this is likely to be associated with a reduction in short-term and long-term ocular complications.;
  - b) The treatment is expected to address a high and urgent unmet clinical need because there are currently no PBS listed treatments specifically for the proposed population; and
  - 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.
- 7.22 The PBAC noted further work is required by the Department to design an age-agnostic single listing of adalimumab in order to finalise the listing.
- 7.23 The PBAC noted this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **8 Recommended listing**

*This restriction is in the process of being finalised. The sponsor will be notified of the final restriction.*

## **9 Context for Decision**

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

## **10 Sponsor's Comment**

AbbVie welcomes the PBAC's recommendation to list adalimumab in vision-threatening uveitis. We would like to acknowledge and thank the clinicians, organisations, patients and family members who supported patient access through providing their invaluable expertise during the submission and consumer comments process.