

**6.01 ADALIMUMAB,
Injection 40 mg in 0.8 mL Pre-Filled Syringe; Injection 40 mg
in 0.8 mL Pre-Filled Pen,
Humira, Abbvie Pty Ltd.**

1 Purpose of Application

1.1 The submission requested an Authority Required PBS listing for adalimumab for the treatment of non-infectious intermediate, posterior or panuveitis.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty (effective) | Proprietary Name and Manufacturer |
|--|----------|-------------|--|-----------------------------------|
| ADALIMUMAB Injection, 40mg in 0.8mL pre-filled syringe, 2 | 1 | 6 | \$ [REDACTED] (\$ [REDACTED]) | Humira® AbbVie |
| ADALIMUMAB Injection, 40mg in 0.8mL pre-filled pen, 2 | 1 | 6 | \$ [REDACTED] (\$ [REDACTED]) | |

| | |
|------------------------------------|---|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Ocular inflammation of a severity that is v vision threatening |
| Condition: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| PBS Indication: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| Treatment phase: | Initial treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency (for severe vision threatening ocular inflammation) <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Treatment criteria: | Must be treated by <i>an ophthalmologist or in consultation with an ophthalmologist with expertise in uveitis</i> |
| Clinical criteria: | Patient must have non-infectious, intermediate, posterior or panuveitis, that is vision threatening with the diagnosis confirmed by an ophthalmologist; AND 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 ≤ 7.5 mg/day while on immunomodulatory therapy; OR |

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| | <p>Patient has severe, vision-threatening ocular inflammation requiring rapid control; OR</p> <p>Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contraindication to corticosteroid and/or immunomodulatory therapy</p> <p>AND</p> <p><i>Treatment must not exceed 24 weeks under this restriction</i></p> |
| Population criteria: | <p>Vision threatening disease is defined as any of at least 1 of the following:</p> <p>a) A decrease in visual acuity of at least 15 letters using an early treatment diabetic retinopathy study (ETDRS) chart or equivalent;</p> <p>b) A two-step increase in anterior chamber cells or vitreous haze</p> <p>c) New retinal vasculitis;</p> <p>d) New retinal or choroidal lesions;</p> <p>e) Other signs of disease progression including visual field changes or electroretinogram changes</p> <p>Severe vision threatening ocular inflammation is defined as any of at least 1 of the following:</p> <p>a) Widespread vascular occlusion;</p> <p>b) Macular threatening retinitis;</p> <p>c) Disease progression on high dose corticosteroids (increasing lesion size and/or new lesions, lack of response according to Standardisation of Uveitis Nomenclature (SUN) criteria for anterior chamber cell and vitreous haze grade as well as visual acuity or further loss of vision despite treatment with corticosteroids at a dose of >40mg/day).</p> |
| Prescriber Instructions | <p>A maximum of 24 weeks treatment will be authorised under this criterion.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> |

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|---|-------------|----------------|----------------------------------|-----------------------------------|
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| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Ocular inflammation of a severity that is v Vision threatening |
| Condition: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| PBS Indication: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| Treatment phase: | Continuing treatment |

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| | |
|------------------------------------|---|
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Treatment criteria: | Must be treated by <i>an ophthalmologist or in consultation with</i> an ophthalmologist with expertise in uveitis |
| Clinical criteria: | <p>Patient must have a documented history of non-infectious, intermediate, posterior or panuveitis that is vision threatening;</p> <p>AND</p> <p>Patient must have previously been issued with a prescription for this drug for this condition;</p> <p>AND</p> <p>Patient has demonstrated a clinical response as defined by <i>at least 1 of the following</i>:</p> <ul style="list-style-type: none"> 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 b) Sustained quiescence of inflammation defined as Standardisation of Uveitis Nomenclature (SUN) criteria $\leq 0.5+$ anterior chamber or vitreous haze, absence of active vitreous or retinal lesions or vitreous cells; or c) Significant reduction from baseline of uveitis cystoid macular oedema by central macular thickness (CMT) on optical coherence tomography (OCT) defined as a 20% reduction in baseline CMT or a reduction of CMT to $\leq 350\mu\text{m}$; or d) Sustained steroid sparing effect, allowing reduction in prednisone to $< 7.5\text{mg}$ daily; or e) Reduction in frequency of ocular attacks to $\leq 1/\text{year}$ (patients with Behcet's disease only) <p>AND</p> <p><i>Treatment must not exceed 24 weeks under this restriction</i></p> |
| Prescriber Instructions | <p>The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to the Department of Human Services no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.</p> <p>Patients are eligible to receive an additional 24 weeks of treatment with this drug providing they demonstrate a response as described above.</p> <p>A maximum of 24 weeks treatment will be authorised under this criterion, noting that the patient does not need to fill all repeats.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> |

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| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Ocular inflammation of a severity that is v vision threatening |
| Condition: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| PBS Indication: | Non-infectious, intermediate, posterior or panuveitis vision threatening uveitis |
| Treatment phase: | Initial PBS-subsidised treatment in a patient who has previously received non-PBS subsidised therapy with this drug (grandfather) |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Treatment criteria: | Must be treated by <i>an ophthalmologist or in consultation with an ophthalmologist with expertise in uveitis</i> |
| Clinical criteria: | Patient must have <i>previously received non-PBS subsidized treatment</i> been receiving treatment with this drug for this condition prior to 1 [month and year]; AND <i>Patient must be receiving treatment with this drug for this condition at the time of application</i> AND Patient must have had a documented history of non-infectious, intermediate, posterior or panuveitis that was considered vision threatening; AND Patient must have demonstrated a clinical response as defined by <i>at least 1 of the following</i> : <ul style="list-style-type: none"> 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 b) Sustained quiescence of inflammation defined as Standardisation of Uveitis Nomenclature (SUN) criteria $\leq 0.5+$ anterior chamber or vitreous haze, absence of active vitreous or retinal lesions or vitreous cells; or c) Significant reduction from baseline of uveitis cystoid macular oedema by CMT on OCT; or d) Sustained steroid sparing effect, allowing reduction in prednisone to <7.5mg daily; or e) Reduction in frequency of ocular attacks to ≤ 1/year (patients with |

| | |
|--------------------------------|--|
| | <p>Behcet's disease only)</p> <p>AND</p> <p><i>Treatment must not exceed 24 weeks under this restriction</i></p> |
| Population criteria: | <p>Vision threatening disease is defined as any of <i>at least 1 of the following:</i></p> <p>a) A decrease in visual acuity of at least 15 letters using an early treatment diabetic retinopathy study (ETDRS) chart or equivalent;</p> <p>b) A two-step increase in anterior chamber cells or vitreous haze</p> <p>c) New retinal vasculitis;</p> <p>d) New retinal or choroidal lesions;</p> <p>e) Other signs of disease progression including visual field changes or electroretinogram changes</p> <p>Severe vision threatening ocular inflammation is defined as any of <i>at least 1 of the following:</i></p> <p>a) Widespread vascular occlusion;</p> <p>b) Macular threatening retinitis;</p> <p>c) Disease progression on high dose corticosteroids (increasing lesion size and/or new lesions, lack of response according to Standardisation of Uveitis Nomenclature (SUN) criteria for anterior chamber cell and vitreous haze grade as well as visual acuity or further loss of vision despite treatment with corticosteroids at a dose of >40mg/day).</p> |
| Prescriber Instructions | <p>The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to the Department of Human Services no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.</p> <p>Patients are eligible to receive an additional 24 weeks of treatment with this drug providing they demonstrate a response as described above.</p> <p>A maximum of 24 weeks treatment will be authorised under this criterion.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> |

2.2 The listing was requested on a cost-effectiveness basis compared to placebo.

2.3 Optical coherence tomography (OCT) was included in the restriction response criteria to measure uveitis cystoid macular oedema by central macular thickness. In March 2016 (66th meeting) MSAC advised that the evidence provided for multiple applications to list OCT on the MBS was supportive for the use of OCT for diagnosis but not for monitoring. Given this advice from MSAC, the following options were proposed for the sponsor to consider:

- (i) Explore whether there is strong enough evidence for new technologies for OCT to support an MSAC application requesting OCT be used to monitor treatment with adalimumab in uveitis, according to the proposed PBS listing;
- (ii) Alter the PBS restriction so that OCT is not part of the restriction response criteria and provide alternative ways to monitor response.

The Pre-Sub-Committee Response (PSCR) (p3) acknowledges that despite OCT being the gold standard for objective assessment of cystic macular oedema associated with uveitis, it is one of five possible criteria for demonstrating response, and therefore the sponsor proposed removing it from the restriction if an MSAC

application is considered necessary. The PBAC considered that given there were other clinical criteria to measure response to adalimumab, OCT could be removed from the restriction.

- 2.4 Uveitis is known to be associated with other systemic immune diseases such as rheumatoid arthritis, ulcerative colitis and psoriasis. The proposed restriction for uveitis does not exclude patients with other systemic diseases that are treated with bDMARDs and 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. The pre-PBAC response (p2) proposed a risk share agreement with subsidisation caps to manage uncertainties to ensure access to the appropriate patients.
- 2.5 The PBAC discussed that the request for emergency provision arrangements for this listing was based on a misinterpretation of the Authority required arrangements. The provision to request Authority approval for emergency arrangements is a mechanism to allow prescribers to obtain Authority approval when the Department of Human Services PBS Authority approvals enquiry lines are unable to take calls because of system issues. Patients requiring emergency treatment should present to emergency departments of hospitals. Therefore emergency medication is likely to be supplied by hospitals rather than under the PBS. The pre-PBAC response (p2) proposed removing the emergency pathway for this patient subpopulation from the PBS restriction wording.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Adalimumab was registered on the ARTG 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.
- 3.2 Adalimumab had not previously been considered by the PBAC for this indication.

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

4 Clinical place for the proposed therapy

- 4.1 Non-infectious intermediate, posterior and panuveitis are a group of vision-threatening diseases that are characterised by intraocular inflammation. Current treatment includes oral corticosteroids and immunomodulatory therapy.
- 4.2 The submission positioned adalimumab as an alternative treatment for non-infectious intermediate, posterior and panuveitis in patients who have failed treatment with a corticosteroid and an immunomodulatory therapy, who require emergency treatment

for severe vision threatening disease, or who are intolerant or contraindicated to corticosteroids and/or immunomodulatory therapy.

- 4.3 The PBAC considered there is a clinical need for patients with non-infectious intermediate, posterior and panuveitis.

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

5 Comparator

- 5.1 The submission nominated current standard of care (consisting of high dose oral corticosteroids (>7.5mg/day) with or without an immunomodulatory agent) as the main comparator. The ESC agreed this was the appropriate comparator.

- 5.2 The PBAC accepted this was the appropriate comparator but noted that the clinical evidence presented did not directly show the effects of adalimumab when corticosteroids were being used, or the incremental benefit over other immunomodulatory agents. Mandatory taper schedules for corticosteroid doses were followed in both trials; all prednisone use was discontinued by week 15 in VISUAL I and between weeks 13–19 in VISUAL II.

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 reiterated that uveitis was the third leading cause of preventable blindness. Although non-infectious intermediate, posterior or panuveitis was less common, it caused a disproportionate level of disability, particularly in those of working age. The clinician presented a case study which highlighted the benefits of adalimumab including the reduction in corticosteroid needed and the patient's improved quality of life.

- 6.2 The clinician addressed other matters in response to the PBAC's questions. The most severe cases require two to three courses of corticosteroids per year. On average, uveitis stabilises after two years, and treatment with adalimumab would be tapered at that point; with most ocular complication having occurred within this period. Corticosteroid doses are slowly tapered to reduce the adverse effects of long term corticosteroid use. Currently, there is a small number of patients in Australia, with around 1-2 patients accessing adalimumab each month. Although almost all patients will experience flare, based on a retrospective cohort study (Dick et al 2016) patients with non-infectious intermediate, posterior and pan-uveitis had a 57.8% risk of developing any ocular complications compared with 16.7% in matched controls (p<0.0001).

- 6.3 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adalimumab including reducing the use of corticosteroids which in turn could reduce the side effects associated with these drugs, and reducing vision impairment.
- 6.5 The PBAC noted the advice received from the Royal Children’s Hospital Melbourne outlining the likely use of adalimumab in the paediatric population in clinical practice. The PBAC noted the different dose for the paediatric population and that patients can be weaned off adalimumab after 6 months of stabilising the uveitis. The Royal Victorian Eye and Ear Hospital and the Royal Australian and New Zealand College of Ophthalmologists were also supportive of adalimumab being made available on the PBS for non-infectious vision threatening intermediate, posterior or panuveitis. Both organisations noted this is the first TGA approved medication specifically for this disease indication.

Clinical trials

- 6.6 The submission was based on two head-to-head trials comparing adalimumab to placebo, with standard of care used in both arms (oral corticosteroid with or without immunomodulatory therapy), in patients with non-infectious intermediate uveitis, posterior uveitis and panuveitis (VISUAL I and VISUAL II), with additional long term data provided from an open label extension study (VISUAL III).
- 6.7 Details of the trials presented in the submission and the supportive longer term comparison are provided in the table below.

Table 1: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|-----------------------------------|--|--|
| Direct randomised trial(s) | | |
| M10-877 (VISUAL I) | 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. 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. | 23 July 2015 New England Journal of Medicine 2016; 375(10): 932-943 |
| M10-880 (VISUAL II) | A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Controlled Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients. 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. | 3 August 2015 The Lancet 2016; 388(10050): 1183-1192 |
| M11-327 (VISUAL III) | Interim analyses of OLE M11-327 | Conference presentation |

Source: Table B.2-2, p.58 of the submission

6.8 The key features of the included studies are summarised in the table below.

Table 2: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome | Use in modelled evaluation |
|----------------------------------|-----|---|--------------|---|-----------------------------------|----------------------------|
| Adalimumab versus placebo | | | | | | |
| VISUAL I | 117 | MC, R, DB, PC 2 treatment arms Up to 80 weeks | Low | Non-infectious intermediate, posterior or panuveitis with active (flaring) disease | Time to treatment failure (flare) | Hazard ratio |
| VISUAL II | 226 | MC, R, DB, PC 2 treatment arms Up to 80 weeks | Low | Non-infectious intermediate, posterior or panuveitis with controlled disease on high doses (10-35mg/day) oral corticosteroids | Time to treatment failure (flare) | Not used |

DB, double blind; MC, multi-centre; PC, placebo controlled; R, randomised.

Source: Compiled during the evaluation

6.9 The primary efficacy outcome was the time to treatment failure (flare). This was a composite outcome consisting of four 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)
- Worsening of best corrected visual acuity by ≥ 15 letters relative to baseline (Early Treatment Diabetic Retinopathy Study chart).

6.10 The long-term clinical relevance of this outcome is unknown. Whilst these measures are used in clinical practice to assess ocular inflammation, the link between the four outcomes used to define flare, and rate of downstream ocular complications such as cataract, visual disturbance, glaucoma or blindness is uncertain. The ESC discussed that ocular complications are thought to be associated with duration, severity and location of uveitis. Given that there was no evidence in relation to the severity of inflammation and only the time to flare was considered in the submission, there are potential unknown impacts on long-term ocular complications, which flow through to the economic model. The pre-PBAC response (p1) argued that chronic non-infectious intermediate, posterior and panuveitis causes cumulative damage to the eye(s) which results from repeated inflammatory attacks on ocular tissues and may be greater than the sum of the individual inflammatory episodes and lead to irreversible consequences. The PBAC noted uncertainties remain around the extrapolation of the efficacy of the surrogate (flares) to the efficacy against complications.

6.11 In the included studies:

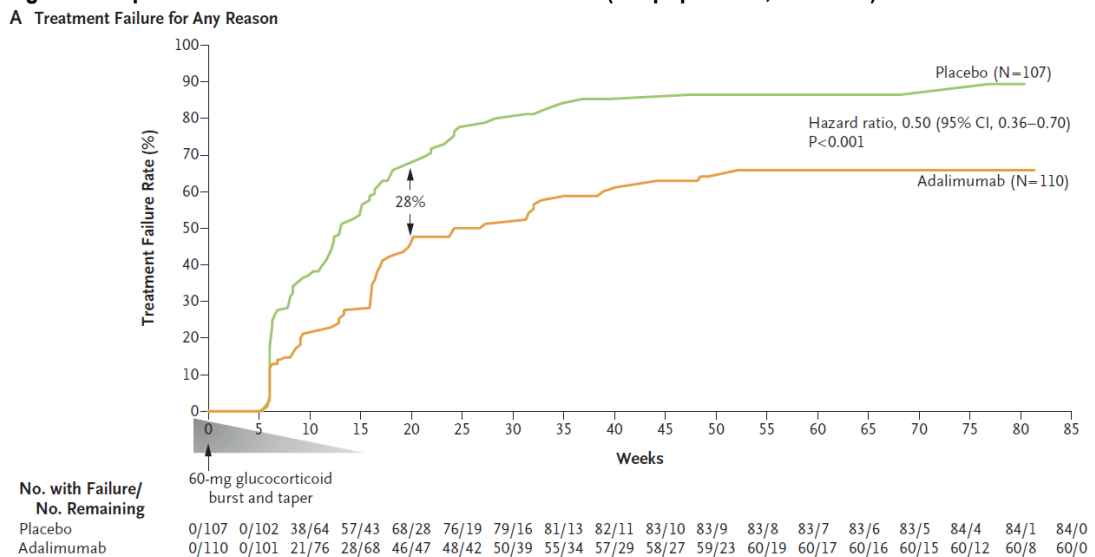
- Patients underwent forced rapid tapering of oral corticosteroids regardless of clinical response, which is not representative of clinical practice.
- Only a proportion of patients (approximately 31% in VISUAL I and 47% in VISUAL II) were taking immunomodulatory therapy at baseline.

6.12 The trial ITT populations were therefore not representative of the eligible population under the requested listing.

Comparative effectiveness

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

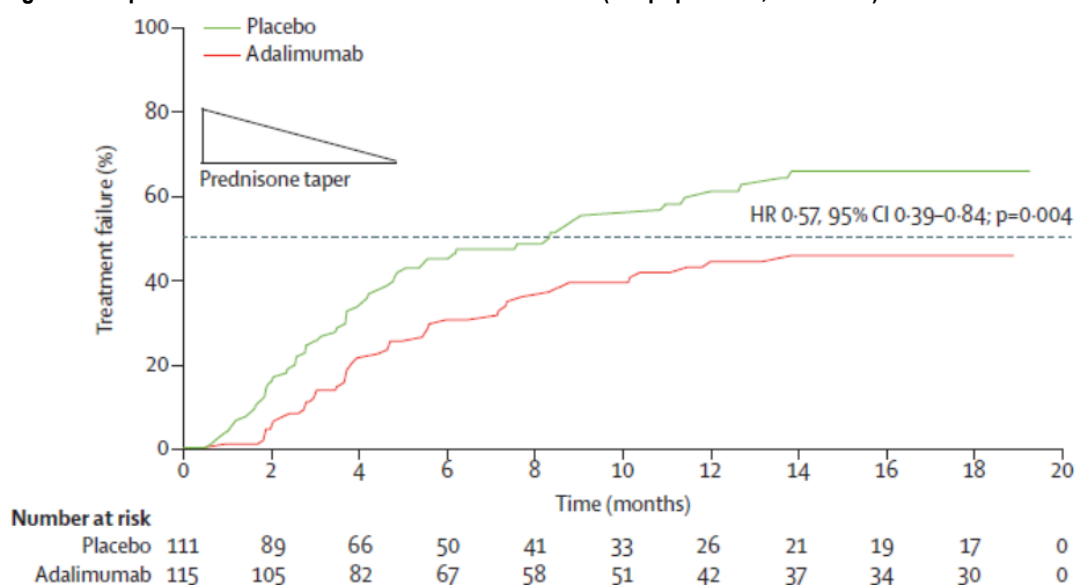
Figure 1: Kaplan-Meier curves of time to treatment failure (ITT population; VISUAL I)



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

- 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; HR 0.50, 95% CI: 0.36, 0.70). The ESC noted that participants in VISUAL 1 were undergoing an active flare at baseline, so ‘treatment failure’ represents worsening of that flare or a new flare. Tapering of corticosteroids also coincides with a difference in flares between adalimumab and placebo.
- 6.15 Time to treatment failure (primary outcome) with adalimumab and placebo from VISUAL II is summarised in Figure 2 below.

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



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

- 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). The ESC noted that participants in VISUAL II did not have an ‘active flare’ at baseline but were dependent on high dose steroids. Therefore, ‘treatment failure’ represents a new flare or recurrence of the original one.
- 6.17 In both studies, there was a statistically significant benefit in favour of adalimumab for time to treatment failure. However, both studies included a forced taper schedule for concomitant oral corticosteroids, currently the mainstay of treatment for ocular inflammation, in both treatment groups regardless of levels of disease activity. In clinical practice assessment of ocular inflammation is performed at each dose reduction. The forced corticosteroid taper schedules used in VISUAL I and VISUAL II may have overestimated the treatment effect of adalimumab. The ESC noted there is no long term use of steroids in the trial so there is no direct data to inform the model of the relative efficacy or safety of adalimumab versus chronic steroids. Overall, the ESC deemed that there was an issue in terms of the applicability of the trial evidence, particularly as the forced tapering may have led to increased flares (more likely to be observed in the placebo arm). The PBAC agreed with the ESC and noted

there is no direct evidence of adalimumab compared to corticosteroid or other immunomodulatory treatment to determine the effectiveness and safety of adalimumab compared to standard care in uveitis.

- 6.18 The ESC also noted some inconsistency across the trials in the quality of life reported using the Visual Function Questionnaire (VFQ-25). In VISUAL I both treatment groups reported worse vision-related functioning from week 6 to the final study visit (see Table 3), whereas in VISUAL II, patients in both treatment groups reported an improvement in vision-related functioning from baseline to the final study visit (see Table 4). Another inconsistency in the VISUAL I trial was the relative improvement on the ocular pain subscore compared with reported adverse events which show adalimumab having a statistically significantly higher proportion of patients reporting eye pain.

Table 3: Change in Visual Function Questionnaire (VFQ-25) composite and subscores from best state achieved prior to week 6 to final visit (VISUAL I)

| | Mean difference from week 6 score (SE) | | Mean difference between treatments (95% CI) |
|--------------------------|--|-----------------|---|
| | Adalimumab (N=101) | Placebo (N=102) | |
| Total score | -1.30 (1.1) | -5.50 (1.2) | 4.20 (1.02, 7.38) |
| Subscore distance vision | ■ (■) | ■ (■) | 1.86 (-2.03, 5.75) |
| Subscore near vision | ■ (■) | ■ (■) | 5.12 (0.34, 9.90) |
| Subscore ocular pain | ■ (■) | ■ (■) | 10.02 (4.86, 15.19) |

Source: Table B.6-9, p.99 of the submission

Notes: The subscale scores of the VFQ-25 are calculated by summing the relevant items and transforming the raw scores into a 0 to 100 scale where higher scores indicate better functioning or well-being. The total score of the NEI VFQ-25 is an average of 11 subscale scores, excluding the single-item general health subscale. Higher scores or increases in score indicate better vision-related functioning.

Table 4: Change in Visual Function Questionnaire (VFQ-25) composite and subscores from baseline to final visit (VISUAL II)

| | Mean difference from baseline score (SE) | | Mean difference between treatments (95% CI) |
|--------------------------|--|-----------------|---|
| | Adalimumab (N=115) | Placebo (N=109) | |
| Total score | 3.36 (1.1) | 1.24 (1.0) | 2.12 (-0.84, 5.08) |
| Subscore distance vision | ■ (■) | ■ (■) | 1.88 (-2.53, 6.29) |
| Subscore near vision | ■ (■) | ■ (■) | -0.10 (-4.81, 4.61) |
| Subscore ocular pain | ■ (■) | ■ (■) | 0.56 (-4.56, 5.68) |

Source: Table B.6-9, p.99 of the submission

Notes: The subscale scores of the VFQ-25 are calculated by summing the relevant items and transforming the raw scores into a 0 to 100 scale where higher scores indicate better functioning or well-being. The total score of the NEI VFQ-25 is an average of 11 subscale scores, excluding the single-item general health subscale. Higher scores or increases in score indicate better vision-related functioning.

Comparative harms

- 6.19 Adalimumab was associated with a higher rate of any infection, active or latent tuberculosis, non-melanoma skin cancers, any malignancy and treatment emergent allergic reactions compared to placebo. The majority of adverse events were mild to moderate in severity and were consistent with the known safety profile of adalimumab.

- 6.20 Based on an expanded assessment of harms, important identified risks associated with adalimumab include serious infections, reactivation of hepatitis B, pancreatitis, lymphoma, hepatosplenic T-cell lymphoma, leukaemia, non-melanoma skin cancer, melanoma, and demyelinating disorders including multiple sclerosis and Guillain-Barre syndrome.
- 6.21 It is possible that there is an increased risk of demyelinating illness when adalimumab is used for uveitis. Demyelinating illnesses (e.g. multiple sclerosis, Guillain-Barre syndrome) have been observed in around █% of patients treated with TNF antagonists. The risk is further increased in patients with uveitis, as up to █% of patients with uveitis (particularly pars planitis or intermediate uveitis, and particularly when associated with periphlebitis) develop multiple sclerosis. The TGA delegate's file note suggested that neurological examination be a requirement before subsidy for intermediate uveitis. The ESC considered that neurological monitoring prior to and during treatment was important to inform initiation and cessation of treatment. The pre-PBAC response (p2) argued that additional neurological screening prior to treatment with adalimumab is required only in patients with non-infectious intermediate uveitis, which is consistent with the TGA approved Product Information for adalimumab. The response also stated that the education programme agreed with the TGA will highlight the known association between intermediate uveitis and demyelinating disorder.

Benefits/harms

- 6.22 A summary of the comparative benefits and harms for adalimumab versus placebo is presented in Table 5 below.

Table 5: Summary of comparative benefits and harms for adalimumab and placebo

| Benefits | Adalimumab | Placebo | Absolute Difference | HR (95% CI) |
|---|---------------------------|------------------------|---|-------------------|
| VISUAL I | | | | |
| Treatment failure | 60/110 (54.5%) | 84/107 (78.5%) | 2.6 months | 0.50 (0.36, 0.70) |
| Median time to treatment failure (months) | 5.6 | 3.0 | | |
| VISUAL II | | | | |
| Treatment failure | 45/115 (39.1) | 61/111 (55.0) | - | 0.57 (0.39, 0.84) |
| Median time to treatment failure (months) | NE | 8.3 | | |
| Harms | Adalimumab n/N | Placebo n/N | Event rate per 100 patient years¹ | |
| | | | Adalimumab | Placebo |
| Any infection | █ | █ | █ | █ |
| Tuberculosis | 4/226 | 1/226 | 3.2 | 0.9 |
| Malignancies | 2/226 | 0/226 | 1.9 | 0 |

Source: Table B.6-1, p.89; Table B.6-11 of the submission; Table 14.3__1.2.M VISUAL I trial report; Table 14.3__1.2.M VISUAL II trial report

¹ In VISUAL I, 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.

- 6.23 On the basis of the direct evidence from the VISUAL I trial presented in the submission, 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. 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 oral corticosteroids to maintain remission.

Clinical claim

- 6.24 The submission described adalimumab as superior in terms of comparative efficacy over current standard of care, and comparable in terms of safety. These claims were not adequately supported for efficacy or safety.
- 6.25 In VISUAL I a large proportion of subjects appeared to meet the criteria for treatment failure at week 6 (first assessment timepoint). This suggests that the initial flare experienced at baseline may have worsened, particularly given the forced tapering of corticosteroids used in the study. As tapering would only occur in clinical practice once inflammation is controlled, this may overestimate the treatment effect of adalimumab.
- 6.26 In VISUAL II patients had stable disease but required high doses of oral corticosteroids to maintain remission and had to follow a mandatory tapering schedule regardless of evidence of inflammation. This is inconsistent with clinical practice, which suggests monitoring for inflammation during corticosteroid tapering. Whilst adalimumab may allow a reduction in corticosteroid use, it is unknown how treatment with adalimumab would compare with continued treatment with oral corticosteroids in this population.
- 6.27 The results from the clinical trials demonstrate that adalimumab has an inferior safety profile to placebo. The adverse event profile of adalimumab, including infections, tuberculosis, cancer and multiple sclerosis, is different to the adverse event profile of oral corticosteroids, which include heart disease, osteoporosis, diabetes and cataracts.
- 6.28 The optimal duration of therapy is unknown. The submission suggested that some patients will be able to cease treatment with adalimumab, however guidance around this is currently limited. The PSCR (p3) provided expert advice suggesting six monthly monitoring and attempt at withdrawal only after two years of quiescence but no data was provided to support this. The PBAC noted from the sponsor hearing that on average, the condition would stabilise after approximately two years of being treated with adalimumab.
- 6.29 The PBAC noted the trial data comparing to adalimumab to placebo in patients refractory to corticosteroids (VISUAL I) demonstrated superior effectiveness for the outcome of treatment failure (flare) and inferior safety; the trial data comparing to adalimumab to placebo in patients intolerant to corticosteroids (VISUAL II) supported potentially superior effectiveness for the outcome of treatment failure (flare) and inferior safety (noting the data does not directly compare to high dose corticosteroids).
- 6.30 The PBAC considered that there was a lack of evidence of the effects of adalimumab compared directly to corticosteroid and other immunomodulatory therapies to support the claims of superior comparative effectiveness and non-inferior comparative safety

to the nominated comparator. Additionally, there were no direct data to demonstrate that the reduction of flares would improve long term outcomes.

Economic analysis

6.31 The submission presented a modelled cost-effectiveness/cost-utility analysis comparing adalimumab to current standard of care (placebo) in patients with uveitis that is non-infectious intermediate, posterior or panuveitis. Patients in both treatment arms receive high dose oral corticosteroids [REDACTED] whenever they experienced an acute ocular complication.

Table 6: Summary of model structure and rationale

| | |
|----------------------------------|---|
| Time horizon | Lifetime (up to [REDACTED] years; a maximum age of [REDACTED]) in the model base case versus up to 80 weeks in VISUAL I trial (median duration of treatment 13 weeks for placebo; 19 weeks for adalimumab). |
| Outcomes | Proportion of patients free of ocular complications; QALYs. |
| Methods used to generate results | Markov cohort analysis. |
| Cycle length | 1 month; half cycle correction. Drug costs were calculated over four weeks; the submission argued this accounts for high, but imperfect compliance. |
| Treatments | Adalimumab, placebo. Patients in both treatment arms receive initial oral corticosteroids, tapered over [REDACTED] months; patients experiencing acute ocular complications also receive corticosteroids, tapered over [REDACTED] months. |
| Health states | [REDACTED] death (all-cause mortality). |
| Transition probabilities | Ocular complications for the placebo arm were derived from Dick et al, 2016 ([REDACTED]); [REDACTED] long-term risk of complications from Dick et al, 2016. All-cause mortality from ABS life tables. |
| Discount rate | 5% for costs and outcomes. |
| Software package | TreeAge Pro 2009. |

Source: constructed during the evaluation

6.32 The long time horizon leads to considerable uncertainty given the lack of an established link between flares and complications; with no data on the impact of adalimumab on ocular complications or consideration of long term adverse events. The submission argued that a long time horizon is necessary as the objective of uveitis treatment is to reduce irreversible vision loss; the benefits of which accrue over the patient's remaining life expectancy. There is considerable uncertainty associated with modelled results over the lifetime time horizon. The duration of the model was tested in sensitivity analysis.

6.33 The economic model does not distinguish between events (and their costs and consequences) affecting one eye and those affecting both eyes. The ESC considered that this was not a major concern given the treatment is systemic and the effects on the utilities used for ocular complications would be minimal.

6.34 The model structure simplified the disease pathway of uveitis. The submission stated that many patients with uveitis that is non-infectious intermediate, posterior or panuveitis experience recurrent episodes of active flaring disease and it is these recurrent episodes of inflammation and the associated cumulative damage, which lead to serious sequelae, including vision loss and blindness. However, the model

does not link active flares to longer-term ocular complications. The probability of ocular complications is derived from a retrospective analysis of US insurance claims data (Dick et al, 2016). It is assumed that the adalimumab treatment effect from VISUAL I (HR=0.5 for risk of inflammatory flare) can be applied to the probability of ocular complications. An individual patient microsimulation model, linking accumulating damage from flares and subsequent ocular complications, may be more appropriate. The ESC also noted that there was a missing link between how change in inflammatory flares would change occurrences of ocular complications. The pre-PBAC response (p3) argues that uveitis is a relatively rare condition and linking all the causal factors for complications and the sequelae of individual flares by severity, location and accumulation of damage is not possible. The PBAC noted that flares and adverse events were not included in the model and long term benefits could not be determined. The PBAC considered that this made the cost effectiveness analysis of the treatment unreliable.

- 6.35 The PBAC considered the model presented in the submission was not reliable for decision making given the overestimation of the treatment effect and other structural issues. Key issues with the economic model are summarised in the table below.

Table 7: Key issues with the model

| Description | Method/Value | Impact |
|--------------------------------------|---|-------------------------------|
| Adalimumab treatment efficacy | <p>The treatment effect for adalimumab was based on the time- to-treatment failure in the VISUAL I trial. This overestimates the relative treatment efficacy of adalimumab compared to placebo due to inadequate background therapy (rapid, forced corticosteroid taper). The submission assumed a 1:1 relationship between the reduction in the time to treatment failure (HR 0.50; VISUAL I trial) and the reduction in the risk of ocular complications (RR ■■■). There are no clinical data to support this claim.</p> <p>The submission applied the treatment effect of adalimumab to the underlying risk of ocular complications in persistent uveitis patients (Dick et al 2016). The use of unadjusted probabilities from persistent uveitis cases was inappropriate as it does not account for the attributable risk due to uveitis and will overestimate the impact of treatment.</p> | Very High, favours adalimumab |
| Adalimumab and corticosteroid safety | <p>The model assumes intermittent use of corticosteroids (at start of model and following ocular complication). This was inconsistent with many of the inputs to the model which were based on long-term treatment with corticosteroids.</p> <p>The model does not account for the long-term adverse effects associated with adalimumab.</p> | Uncertain, favours adalimumab |
| Adalimumab treatment duration | The submission estimated the expected duration of adalimumab therapy based on the proportion of uveitis patients that remain at risk of ocular complications and therefore require treatment (Dick et al 2016). Ocular complications are potential downstream effects of uveitis and are therefore of limited relevance in determining treatment duration. | High, favours adalimumab |
| Time horizon | Lifetime time horizon based on the need to model chronic events with long-term consequences (e.g. blindness). The model is highly dependent on extrapolated data. | High, favours adalimumab |

Source: compiled during the evaluation

- 6.36 The results of the economic evaluation comparing adalimumab and placebo are summarised in Table 8.

Table 8: Results of the modelled economic evaluation

| | Adalimumab | Placebo | Increment |
|-------------------------------------|-------------------|----------------|------------------|
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALY | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/QALY gained | | | \$ [REDACTED] |

Source: Table D.5-1, p178 of the submission

- 6.37 Based on the economic model, treatment with adalimumab was associated with an incremental cost per QALY gained of \$45,000 – \$75,000 compared with placebo (current standard of care).

6.38 The results of key sensitivity analyses are summarised below.

Table 9: results of key sensitivity analyses

| Analysis | Incremental costs | Incremental QALYs | ICER (\$/QALY) |
|--|-------------------|-------------------|----------------|
| Base case | \$ [redacted] | [redacted] | \$ [redacted] |
| VISUAL I hazard ratio (risk of flare; base case: 0.50) | | | |
| - lower 95% limit (0.36) | \$ [redacted] | [redacted] | \$ [redacted] |
| - upper 95% limit (0.70) | \$ [redacted] | [redacted] | \$ [redacted] |
| Relationship between treatment effect from trial based on risk of inflammatory flare and treatment effect applied in the model to ocular complications (base case 1:1) | | | |
| - [redacted] (relative effect [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - [redacted] (relative effect [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| Treatment effect applied to risk attributable to uveitis only | \$ [redacted] | [redacted] | \$ [redacted] |
| Time horizon (base case lifetime/maximum [redacted] years; age [redacted] years) | | | |
| - 10 years | \$ [redacted] | [redacted] | \$ [redacted] |
| - 20 years | \$ [redacted] | [redacted] | \$ [redacted] |
| Annual cost of blindness (base case \$ [redacted]) | | | |
| - increase by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - decrease by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - include indirect costs of blindness (\$ [redacted]/yr) | \$ [redacted] | [redacted] | \$ [redacted] |
| Annual cost of glaucoma (base case \$ [redacted]) | | | |
| - increase by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - decrease by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| Annual cost of retinal disorder (base case \$ [redacted]) | | | |
| - increase by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - decrease by 50% (\$ [redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| Blindness/low vision utility (base case 0.26) | | | |
| - 0.47 (alternative estimate from Brown 2001) | \$ [redacted] | [redacted] | \$ [redacted] |
| - 0.65 (alternative estimate from Brown 2001) | \$ [redacted] | [redacted] | \$ [redacted] |
| Glaucoma utility (base case [redacted]; disutility [redacted]) | | | |
| - increase disutility by 50% ([redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - decrease disutility by 50% ([redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| Retinal disorder utility (base case [redacted]; disutility [redacted]) | | | |
| - increase disutility by 50% ([redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| - decrease disutility by 50% ([redacted]) | \$ [redacted] | [redacted] | \$ [redacted] |
| Disease remission/treatment withdrawal (base case [redacted] % at [redacted] years; [redacted] % at [redacted] years) | | | |
| - annual withdrawal [redacted] % ([redacted] per month; estimate used in financial model) | \$ [redacted] | [redacted] | \$ [redacted] |

Source: Table D.6-1, pp184-186 of the submission and calculations performed during the evaluation using the Adalimumab_uveitis model.

The redacted table shows ICERs in the range less than \$15,000 per QALY to \$105,000/QALY – \$200,000/QALY.

6.39 The economic model was most sensitive to the treatment effect of adalimumab applied to ocular complications, which is associated with considerable uncertainty. The efficacy estimate from VISUAL I may be overestimated due to the forced taper of oral corticosteroids. The assumed 1:1 relationship between reduction in risk of inflammatory flare as measured in the trial between adalimumab and placebo (HR 0.50) from VISUAL I and reduction in probabilities of ocular complications (RR [redacted]) is not supported by data, particularly in terms of the quantitative relationship, and

given the composite nature of the measured endpoint of inflammatory flare. The ESC did not believe it was appropriate to assume that a reduction in risk of any of the measured endpoints directly translated to a reduction in risk of ocular complications.

- 6.40 The use of unadjusted probabilities of complications is inappropriate as it does not account for the attributable risk due to uveitis, overestimating the impact of treatment. The PSCR (pp2-3) contended that according to Dick et al. (2016) it was reasonable to conclude that ocular complications only occur during periods of flare, and a reduction in flare rate would therefore result in corresponding reductions in the incidence of long-term uveitis. The PSCR (pp3-4) also argued the rates and nature of complications with other natural history studies such as the Manchester Uveitis Study suggested the use of unadjusted probabilities was reasonable. However, the ESC considered that this incorrectly assumed there was no underlying risk of ocular complications in these patients apart from uveitis.
- 6.41 The pre-PBAC (p3) response acknowledged that the 1:1 link may overestimate adalimumab's treatment effect. However, it was further noted in the response that quantification of the extent to which unrelated complications would contribute to each arm of the clinical trial and the consequent impact this has on the 1:1 link between the trial endpoint and uveitis complications ratio used in the model is uncertain. The pre-PBAC response (p3) noted from Dick et al (2016) (for the persistent NIIPPU group), 5 year risks of 83.3% and 26.7% for any ocular complication are reported for the disease and control groups respectively. This can be interpreted as ■% of ocular complications are attributable to uveitis (flare) [$1 - (\frac{\text{■}}{\text{■}} / \frac{\text{■}}{\text{■}})$] and hence potentially avoidable with adalimumab treatment. When the risk reduction from the VISUAL 1 trial (0.5) is applied only to uveitis complications this implies a relative risk across all events of ■ ($= \text{■} \times \text{■} + \text{■} \times \text{■}$). The response proposed a relative risk of ■, halfway between ■ from VISUAL I and ■ from Dick et al (2016). The PBAC did not accept this adjusted probability of ocular complications sufficiently addressed the issue of the attributable risk due to uveitis and the relationship of the risk reduction for flares and long-term ocular complications.
- 6.42 The model included the costs and consequences of adverse events associated with long-term oral corticosteroid use, which likely overestimates these impacts (favouring adalimumab) given the intermittent use of corticosteroids in the model and with the relative efficacy data extracted from the trials, which did not use long term steroids. The ESC further noted that the model did not account for the adverse effects associated with the long-term use of adalimumab (up to ■ years in the model), which include infections, cancer and multiple sclerosis. The PSCR (p4) argued that the adverse event rates were low and there was high level evidence to show that anti-TNFs did not increase the risk of solid cancer in patients without or with prior malignancy.
- 6.43 The model is also sensitive to the time horizon, the costs and utilities of chronic ocular complications and assumptions regarding disease remission and treatment withdrawal. The ESC noted that the utilities in the model were drawn from a range of sources, which may not be applicable and may have resulted in double counting:
- utility for uveitic flare was drawn from the trial (pooled estimate of utility comparing patients with and without flare);
 - utilities for ocular complications were drawn from a range of different sources that do not relate to ocular complications from uveitis;

- disutilities for adverse events associated with corticosteroid treatment are included (but there are no disutilities for adverse events associated with adalimumab). Also these disutilities relied on a DALY (disability-adjusted life-year) approach. Disutility for weight gain is included from a study based on weight gain from HbA1c (although, this had minimal impact).

Drug cost/patient/year:

- 6.44 In the initial year, the estimated annual cost for adalimumab was \$ [REDACTED] based on 27.5 injections per year, equivalent to 13.75 scripts of the maximum quantity (i.e. 2 injections loading dose week 1, followed by 25.5 fortnightly injections for 51 weeks at the effective DPMQ of \$ [REDACTED]).
- 6.45 In continuing years, the estimated annual cost for adalimumab was \$ [REDACTED] based on 26 fortnightly injections per year, equivalent to 13 scripts of the maximum quantity at the effective DPMQ of \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.46 This submission was considered by DUSC.
- 6.47 The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of adalimumab for the treatment on non-infectious intermediate, posterior and panuveitis.

Table 10: Estimated use and financial implications

| | Year 1 (2017) | Year 2 (2018) | Year 3 (2019) | Year 4 (2020) | Year 5 (2021) | Year 6 (2022) |
|--|------------------|------------------|------------------|------------------|------------------|------------------|
| Total number of patients treated per year | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Total number of prescriptions per annum | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Cost of adalimumab (proposed effective DPMQ, \$ [REDACTED] per pack) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Patient copayment (\$28.56) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Net cost to PBS/RPBS (effective price) | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |

Source: Table E.2-1, p.195; Table E.2-2, p.196; Table E.2-3, p.197; Table E.2-4, p.198; Table E.2-5, p.199; Table E.2-6, p.200; Table E.4-1, p.201 of the submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

- 6.48 The estimated financial implications were highly uncertain and the DUSC considered it was likely to be underestimated. The DUSC noted that the estimates were derived from a number of international sources. The DUSC considered this increased the overall uncertainty around the final numbers rather than providing triangulation to verify the appropriateness of the assumptions.

- 6.49 Assumptions regarding estimated uptake and discontinuation rates were also uncertain. Uptake was estimated to start at █% in year 1, increasing to █% by year 2; the low uptake was assumed on the basis of registration of adalimumab in the setting being recent and no international data on uptake being available. The DUSC considered this is a likely underestimate given there are no alternative appropriate therapies for patients who have failed to achieve an adequate response to corticosteroid therapy in combination with at least one immunomodulatory agent. Furthermore, the DUSC considered that the ordering of diagnosis and referral should be reversed. Therefore, the rate of referral following diagnosis is likely to be █% rather than █% used in the estimates.
- 6.50 The DUSC noted that it was unclear if patients who previously had well controlled disease using adalimumab will be able to restart treatment. The DUSC also noted that the proportion of patients with uncontrolled disease is likely to be higher than █%.
- 6.51 The DUSC noted that the requested listing allows treatment in patients under the age of 18 years, but these patients were not included in the financial estimates. The pre-PBAC response (p3) provided revised data which included the paediatric population and a reduced effective DPMQ which changed the cost to government at the end of year 5 to \$10 – \$20 million. To address the concerns around the underestimation of use, the pre-PBAC response (p3) also proposed a rebate of █% in the event that the subsidisation caps were exceeded.

Table 11: Revised net impact to the government (at █ effective DPMQ and including paediatric patients)

| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|--------------------------------------|------|------|------|------|------|------|
| Adult patients treated per year | █ | █ | █ | █ | █ | █ |
| Cost to the Govt. (at eff. DPMQ) | \$█ | \$█ | \$█ | \$█ | \$█ | \$█ |
| Paediatric patients treated per year | █ | █ | █ | █ | █ | █ |
| Cost to the Govt. (at eff. DPMQ) | \$█ | \$█ | \$█ | \$█ | \$█ | \$█ |
| Total | \$█ | \$█ | \$█ | \$█ | █ | \$█ |

Source: Table 1, pre-PBAC response.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 million - \$20 million.

Quality Use of Medicines

- 6.52 No quality use of medicines issues were identified in the submission. However, the TGA delegate's file note raised safety concerns around the use of adalimumab for treatment of non-infectious uveitis (particularly intermediate uveitis) and the risk of demyelinating disorders. The pre-PBAC response (p2) noted the DUSC's concern about the potential treatment barrier and assured that there is an education programme for ophthalmologists around intermediate uveitis, adalimumab and the increased risk of demyelinating disorders that has been agreed to by the TGA.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of adalimumab for the treatment of non-infectious intermediate, posterior uveitis or panuveitis due to low confidence in the magnitude of the effectiveness compared with current treatment and uncertain cost effectiveness compared to placebo.
- 7.2 The PBAC accepted there was high clinical need for additional effective treatment options for patients who have not achieved adequate response to corticosteroid therapy and immunomodulatory therapy.
- 7.3 The PBAC accepted the rationale of the proposed restriction with the removal of optical coherence tomography as one of the clinical criteria for measuring response for continuing treatment and the inappropriate emergency authority for severe vision threatening disease. However, the PBAC agreed that patients with high risk of vision loss (eg Behcet's disease) should be eligible. The PBAC also 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.
- 7.4 The PBAC accepted current standard care (consisting of high dose oral corticosteroids (>7.5 mg/day) with or without an immunomodulatory agent) as the comparator.
- 7.5 The PBAC noted that VISUAL I and VISUAL II trial data do not directly show the effects of adalimumab compared to corticosteroid use due to the mandatory dose taper schedule for corticosteroids. The majority of the trial evidence is comparing adalimumab to placebo (with or without immunomodulating therapy). As noted in the sponsor hearing, 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. 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.
- 7.6 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.
- 7.7 The PBAC noted that treatment with adalimumab was associated with a statistically significant increase in time to treatment failure compared with placebo (VISUAL I: median time to treatment failure 5.6 months vs. 3 months with placebo; HR 0.50 (0.36, 0.70); VISUAL II: median time to treatment failure not reached vs. 8.3 months with placebo; HR 0.57 (0.39, 0.84)). However, 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.

- 7.8 The PBAC 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 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.
- 7.9 The PBAC noted the increased risk of demyelinating illness when adalimumab is used for uveitis. The PBAC considered that it was appropriate that additional neurological screening prior to treatment with adalimumab is required for patients considered at high risk, which is consistent with the TGA approved Product Information for adalimumab.
- 7.10 The PBAC noted from the sponsor hearing that on average, it took two years for uveitis to stabilise in patients currently being treated with adalimumab. Additionally, patients would be on a further two to three courses of corticosteroids to control re-flares and it would take two to ten years for the ocular complications to reduce. The PBAC noted this was an important consideration when modelling the benefits of adalimumab over time.
- 7.11 The PBAC noted the trial data comparing adalimumab to placebo in patients refractory to corticosteroids (VISUAL I) demonstrated superior effectiveness for the outcome of treatment failure (flare) and inferior safety; the trial data comparing to adalimumab to placebo in patients intolerant to corticosteroids (VISUAL II) supported potentially superior effectiveness for the outcome of treatment failure (flare) and inferior safety (noting the data does not directly compare to high dose corticosteroids). However, the PBAC considered that there was a lack of evidence of the effects of adalimumab compared directly to corticosteroid and other immunomodulatory therapies to support the claims of superior comparative effectiveness and non-inferior comparative safety to the nominated comparator. Additionally, there were no direct data to demonstrate that the reduction of flares would improve long term effects.
- 7.12 The PBAC considered the model presented in the submission was not reliable for decision making given the overestimation of the treatment effect and other structural issues.
- 7.13 The PBAC noted from the sponsor hearing that although almost all patients with non-infectious intermediate posterior or panuveitis will experience flare, only a proportion of patients will go on to experience long-term complications. By not including the occurrence of uveitic flares over time in the model the uncertainty of the relationship between flare and ocular complications was increased. More importantly, applying the more favourable hazard ratio of 0.50 from VISUAL I to the probability of ocular complications on a 1:1 basis was likely to substantially overestimate the treatment benefit. The pre-PBAC response adjusted the probabilities of ocular complications by including the attributable risk associated with uveitis, from the Dick et al (2016) retrospective cohort study. However, the 0.50 hazard ratio was still applied to the

probability of ocular complications, thus retaining the assumption that a 50% reduction in uveitis flares equates to a 50% reduction in uveitis-attributable ocular complications. The PBAC noted that even after accounting for the fact that many ocular complications are not attributable to uveitis, 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.

- 7.14 The PBAC also noted that the model was sensitive to the time horizon. 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.
- 7.15 The PBAC considered the model should include the both the benefits and harms of corticosteroid use. The adverse events of adalimumab also need to be included in the model.
- 7.16 The PBAC acknowledged that there is a clinical place for adalimumab for the treatment of non-infectious intermediate, posterior or panuveitis and would welcome a major resubmission. The PBAC considered that a major resubmission should present a revised economic model which addresses the above concerns, including a clearer link between uveitic flares and ocular complications, a reduction in flares using the relative risks from both VISUAL I and VISUAL II rather than the most favourable result, a more plausible risk of developing ocular complications, a revised time horizon of 10 years, and the inclusion of adverse events of adalimumab and corticosteroid use in the model.
- 7.17 The PBAC noted the DUSC concerns regarding the patient numbers and re-treatment. Combined with overall uncertainty in the cost-effectiveness of use, the PBAC considered a risk share arrangement should include revised financial estimates and a 100% rebate above the agreed cap.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review because the submission was a request to change an existing listing for different disease or condition than the disease or condition for which the medicine is already subsidised.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to

recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

AbbVie welcomes the PBAC's acknowledgement of the unmet clinical need for an effective treatment for patients with non-infectious intermediate, posterior or pan-uveitis, however is disappointed in the PBAC's decision to reject the adalimumab submission for this condition.

In response to PBAC's view noted in section 6.21 and 7.9: "It is possible that there is an increased risk of demyelinating illness when adalimumab is used for uveitis", AbbVie highlights that the association is with the disease rather than the treatment as stated in the TGA approved adalimumab product information "There is a known association between intermediate uveitis and central demyelinating disorders."