

## 6.03 DEXAMETHASONE, Intravitreal implant 700 µg, Ozurdex<sup>®</sup>, Allergan Australia Pty Ltd

### 1 Purpose of application

- 1.1 The submission requested an Authority Required listing for dexamethasone implant for the treatment of non-infectious posterior segment uveitis.
- 1.2 Listing was requested on the basis of a cost utility analysis compared to placebo (standard of care).

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

Component	Description
Population	Patients with non-infectious uveitis affecting the posterior segment of the eye.
Intervention	Dexamethasone intravitreal implant (700 µg)
Comparator	Standard of care (represented by sham with use of rescue medication in the trial). Secondary comparisons with adalimumab and intravitreal triamcinolone acetonide (IVTA)
Outcomes	Improvement in best corrected visual acuity Reduction in use of systemic corticosteroids and immunosuppressants Reduction of vitreous haze Reduction of macular oedema (central retinal thickness)
Clinical claim	In patients with non-infectious posterior segment uveitis, a single dexamethasone implant is significantly more effective than sham in improving intraocular inflammation, visual haze, and visual acuity, with an inferior (but acceptable) safety profile.

Source: Table 1-1, p.2 of the submission

### 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	Nº.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DEXAMETHASONE INTRAVITREAL IMPLANT, 700 MICROGRAM	1	0	\$ [REDACTED]	Ozurdex <sup>®</sup> Allergan
PBS Indication:	Non-infectious uveitis affecting the posterior segment of the eye			
Restriction:	Authority Required – Writing, Telephone, or Electronic			
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.			
Clinical criteria:	Patient must have non-infectious uveitis affecting the posterior segment of the eye. Patient must have documented visual impairment (BCVA ≤ 6/12) secondary to vitreous haze and/or macular oedema.			

- 2.1 The requested restriction does not adequately define the proposed population, and is not consistent with the place in therapy identified in the submission. The Pre-Sub-Committee Response (PSCR, p3) clarified the population for whom listing of dexamethasone implant is sought:

- a) Unilateral/asymmetric/bilateral flare-up with inactive (or controlled) systemic disease

- b) Unilateral/asymmetric flare-up secondary to active systemic disease where further intensification of systemic treatment is not clinically indicated
- c) Bilateral flare-up secondary to active systemic disease where further intensification of systemic treatment is not clinically indicated.

The PSCR (p3) confirmed that in the clinical management algorithm dexamethasone implant will be used as first line therapy in patients under population (a) whereas for population (c) dexamethasone would be used later in the clinical management algorithm. The PSCR (p3) also noted that for population (b), the use of dexamethasone implant may be considered clinically appropriate at an earlier point in the treatment algorithm due to the unilateral/asymmetric presentation of the patient's uveitis (compared with population (c)) to avoid unnecessary intensification of systemic treatment and their inherent side effects. The ESC noted that non-infectious uveitis affecting the posterior segment of the eye was primarily due to an underlying systemic disease but was occasionally idiopathic. The ESC also noted that the systemic treatments referred to by the PSCR include systemic corticosteroids, steroid sparing immunomodulatory therapy and biologics (primarily tumour necrosis factor alpha inhibitors).

- 2.2 The clinical evidence includes primarily patients with unilateral/bilateral disease with inactive systemic disease or no systemic disease (idiopathic uveitis). No clinical evidence was provided in patients who experienced incomplete control in one eye (asymmetric inflammation) or in patients who experienced incomplete control in both eyes and required bilateral implants. The PSCR (p2) argued that patients with asymmetric inflammation, patients with incomplete control in both eyes (in whom bilateral implants would have been indicated [though not able to be used during the trial]), and those with active (but stable) systemic disease were not excluded from recruitment to the HURON trial. However, the ESC considered that the proportion of patients with active systemic disease could not be accurately inferred from rates of systemic corticosteroid use alone, as suggested by the response, since this therapy may be used to treat uveitis in the absence of systemic disease.
- 2.3 The submission suggested dexamethasone implant may be repeated as needed to maintain control. The PSCR (p5) clarified that dexamethasone implant is proposed to be used to treat relapses or recurrence of flare-ups rather than preventing relapse after achieving an improvement (i.e. maintenance of improvement). Patients would need to requalify according to the clinical criteria in order to receive a subsequent implant. The submission did not provide any comparative clinical evidence for repeat treatment with dexamethasone implant. The ESC noted the submission presented data from observational studies investigating outcomes after administration of repeat treatment with dexamethasone implant. In addition, while some attenuation of response may be seen with repeat implants when treating relapses or recurrence of flare-ups, the ESC considered it was not unreasonable to expect that repeat implants in individuals with a prior satisfactory response would have efficacy. The PBAC considered this to be acceptable.
- 2.4 The PSCR (p2) noted that the proposed restriction permits use of dexamethasone implant for posterior segment uveitis, which would include patients with panuveitis,

and that the commentary indicated patients with panuveitis were not included in the HURON trial. The PSCR (p2) claimed that there was a requirement that patients have a diagnosis of intermediate or posterior segment uveitis and patients with panuveitis and patients with anterior uveitis were not excluded from recruitment to the trial. The ESC noted that patients with panuveitis comprise a small proportion of those with non-infectious posterior segment uveitis.

- 2.5 The PBAC considered there is a clinical place for dexamethasone implant in the treatment of non-infectious uveitis affecting the posterior segment of the eye given the gap in available treatment for these patients.
- 2.6 The PBAC noted the pre-PBAC response (p1) did not propose new restriction wording. The PBAC recommended that the dexamethasone implant be PBS listed for unilateral/bilateral flare of non-infectious posterior segment uveitis where systemic therapy or further intensification of systemic therapy is not required or contraindicated and where there is documented visual impairment (BCVA  $\leq$  6/12) secondary to vitreous haze and/or macular oedema.
- 2.7 The PBAC recommended an Authority Required (Telephone) listing for dexamethasone implant for the treatment of non-infectious posterior segment uveitis.

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

### **3 Background**

#### **Registration status**

- 3.1 TGA status at time of PBAC consideration: Dexamethasone implant was granted orphan drug designation by the TGA for 'the treatment of non-infectious uveitis affecting the posterior section of the eye' on 12 April 2017. Dexamethasone implant was TGA registered on 16 June 2017 for non-infectious uveitis affecting the posterior segment of the eye.
- 3.2 Dexamethasone implant is also TGA registered for diabetic macular oedema, and macular oedema due to branch retinal vein occlusion or central retinal vein occlusion.

#### **4 Population and disease**

- 4.1 Non-infectious intermediate, posterior and panuveitis (non-infectious posterior segment uveitis) are a group of vision-threatening diseases that are characterised by intraocular inflammation.
- 4.2 Non-infectious uveitis may be idiopathic or associated with systemic autoimmune diseases. Regardless of the underlying aetiology, persistent intraocular inflammation can lead to ocular complications and even blindness if left untreated.
- 4.3 Non-infectious posterior segment uveitis has a relatively early onset and the incidence is highest in working-age people.

- 4.4 Current treatments include oral, intravitreal, or periocular corticosteroid therapy, and corticosteroid-sparing immunomodulatory therapy and biologics in some cases.
- 4.5 The submission claimed that dexamethasone implant will primarily replace current intravitreal triamcinolone acetonide, which is currently used as second or first line therapy in local and/or unilateral disease.
- 4.6 The submission also positions dexamethasone implant as an adjunct to systemic therapy to reduce steroid or steroid-sparing therapy usage. Systemic treatment may be required for patients with bilateral uveitis who more commonly have active systemic disease. Dexamethasone implant has a role in bilateral disease if it is asymmetrical in severity – for example after one eye responds better than the other to systemic therapy. No specific comparative clinical evidence was provided for dexamethasone implant in uveitis accompanied by systemic disease, or as maintenance therapy in inactive disease. The PSCR (p5) clarified that the submission is not seeking listing for maintenance treatment, but only use of dexamethasone implant for the treatment of flare-ups (including treatment of relapse/recurrence) of uveitis. The PBAC considered this was appropriate.

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

## **5 Comparator**

- 5.1 The submission nominated placebo (standard of care) as the main comparator. In the key trial, standard of care included the use of rescue medications only (including administration of intravitreal/periocular injections of corticosteroids or systemic medications) immediately upon worsening of intraocular inflammation. The therapy most likely to be replaced in clinical practice is intravitreal, periocular, or systemic corticosteroids. Efficacy outcomes for patients who received corticosteroids (periocular, intravitreal, or systemic) as rescue medication in the HURON trial were not recorded as censoring occurred in both arms of the trial at the point of rescue therapy being required. As a result the PBAC considered the sham treatment arm in the HURON trial may not represent current true standard of care for posterior segment uveitis.
- 5.2 The submission nominated intravitreal triamcinolone acetonide as a secondary comparator. The submission claimed that in patients with predominantly unilateral/asymmetric disease (either idiopathic or with inactive systemic disease), patients with bilateral flare-up with inactive systemic disease, and in patients with uveitis who have active systemic disease but are on maximal systemic therapy, dexamethasone implant may replace unregistered or off-label intravitreal triamcinolone acetonide to treat ocular flare-ups in clinical practice. The PBAC considered this was an appropriate secondary comparator.
- 5.3 The submission nominated adalimumab as a secondary near market comparator. A submission to list adalimumab for non-infectious intermediate, posterior or pan-uveitis on the PBS was rejected at the March 2017 PBAC meeting. Dexamethasone implant and adalimumab are likely to be used in different populations with non-infectious posterior segment uveitis, and as such the PBAC considered the usefulness of this comparison to be limited.

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

## 6 Consideration of the evidence

### Sponsor hearing

6.1 There was no hearing for this item.

### Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (7), health care professional (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dexamethasone implant over systemic treatment and intravitreal triamcinolone. These included improvements in vision over a longer duration along with a reduction in side effects and the number of specialist visits required.

6.3 The PBAC noted the correspondence received from The Royal Australian and New Zealand College of Ophthalmologists (RANZCO) supporting the use of dexamethasone implant in clinical practice. The PBAC specifically noted that uveitis is the most common cause of vision loss in people of working age. RANZCO indicated the side effect profile of dexamethasone was tolerable, and the medication lasts for between 4–6 months. Additionally, RANZCO indicated that the slow release profile of this drug is particularly useful in patients who have had a vitrectomy. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### Clinical trials

6.4 The submission is based on one head-to-head randomised trial comparing a single dexamethasone implant to placebo (sham) in patients with non-infectious posterior segment uveitis (HURON).

6.5 The submission also included two supplementary comparisons:

- Indirect comparison of dexamethasone implant to intravitreal triamcinolone acetonide (Shin et al., 2015) in non-infectious posterior segment uveitis.
- Indirect comparison of dexamethasone implant to adalimumab (VISUAL I) in non-infectious posterior segment uveitis.

6.6 Details of the trials presented in the submission are provided in the table below.

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

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
HURON (Trial 014)	Clinical Study Report 206207-0 14: An 8-Week, Multicentre, Masked, Randomized Trial (with an 18-Week Masked Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System Compared with Sham DEX PS DDS Applicator System in the Treatment of Non Infectious Ocular Inflammation of the Posterior Segment in Patients with Intermediate or Posterior Uveitis  Lowder et al. Dexamethasone Intravitreal Implant for Non-infectious Intermediate or Posterior Uveitis  Lightman et al. Vision-Related Functioning Outcomes of Dexamethasone Intravitreal Implant in Noninfectious Intermediate or Posterior Uveitis  Naik et al. Normative Comparison of Patient-Reported Outcomes in Patients With Noninfectious Uveitis	22 September 2009  Arch Ophthalmol. 2011;129(5):545-553  Invest Ophthalmol Vis Sci. 2013;54:4864–4870  JAMA Ophthalmol. 2013;131(2):219-225
<b>Supplementary randomised trials</b>		
VISUAL I	Jaffe et al. Adalimumab in Patients with Active Noninfectious Uveitis  Sheppard et al. Effect of Adalimumab on Visual Functioning in Patients With Noninfectious Intermediate Uveitis, Posterior Uveitis, and Panuveitis in the VISUAL-1 and VISUAL-2 Trials	N Engl J Med 2016;375:932-43  JAMA Ophthalmol. 2017. doi:10.1001/jamaophthalmol.2017.0603
Shin et al. 2015	Intravitreal Triamcinolone Injection for Uveitic Macular Edema: A Randomized Clinical Study	Ocular Immunology & Inflammation 2015; 23(6):430–436

Source: Table 2-3, p.41 of the submission; Table 3, p.8 of Appendix 1 of the submission; and Table 3, p.6 of Appendix 2 of the submission

6.7 The key features of the direct randomised trials are summarised in the table below.

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

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Dexamethasone implant versus sham</b>						
HURON	229	Randomised, double blind 26 weeks	Low	Non-infectious posterior or intermediate uveitis	Proportion achieving vitreous haze score of 0; improvement in BCVA	Proportion achieving gain in BCVA of ≥ 5, 10 or 15 letters; peak letters gained weeks 6-12
<b>Intravitreal triamcinolone acetate versus sham</b>						
Shin et al. (2015)	50	Randomised, double blind 6 months	High	Non-infectious uveitis complicated by macular oedema	Change in retinal thickness, change in BCVA, inflammatory control	Not used
<b>Adalimumab versus placebo</b>						
VISUAL I	223	Randomised, double blind 80 weeks	Low	Patients with active non-infectious intermediate, posterior or panuveitis	Time to treatment failure at or after week 6, change in BCVA, evidence of macular oedema	Not used

Source: compiled during the evaluation from HURON clinical trial report and relevant publications (Shin et al, 2015; Jaffe et al., 2016)  
Abbreviations: BCVA, best corrected visual acuity

6.8 The PBAC considered the HURON trial to have a low risk of bias.

**Comparative effectiveness**

6.9 The proportion of patients achieving a vitreous haze score of 0 at each visit is summarised in Table 4 below. The primary outcome for the HURON trial was the proportion of patients achieving a vitreous haze score of 0 at week 8.

**Table 4: Proportion of patients achieving a vitreous haze score of 0 in the HURON trial (ITT)**

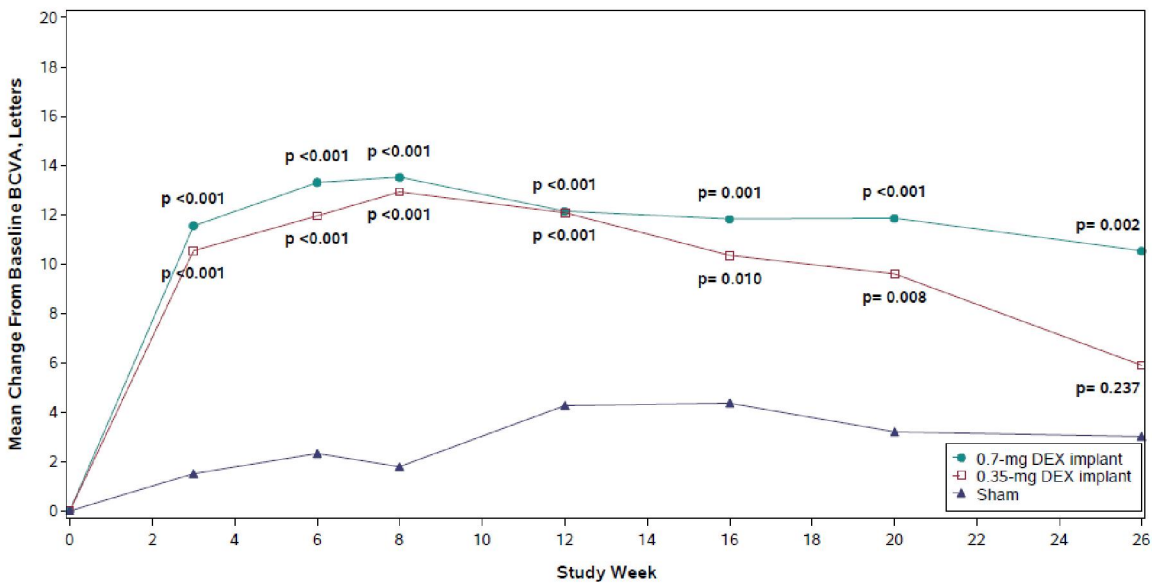
Study visit	Patients with vitreous haze score of 0, n/N (%)			Dexamethasone 700 µg implant vs. sham % difference (95% CI)
	Dexamethasone 700 µg implant	Dexamethasone 350 µg implant	Sham	
Week 3	18/77 (23.4)	11/76 (14.5)	9/76 (11.8)	11.5 (-0.4, 23.5)
Week 6	33/77 (42.9)	23/76 (30.3)	7/76 (9.2)	33.6 (20.8, 46.5)
Week 8	36/77 (46.8)	27/76 (35.5)	9/76 (11.8)	34.9 (21.6, 48.2)
Week 12	35/77 (45.5)	32/76 (42.1)	10/76 (13.2)	32.3 (18.8, 45.8)
Week 16	31/77 (40.3)	25/76 (32.9)	16/76 (21.1)	19.2 (4.9, 33.5)
Week 20	30/77 (39.0)	32/76 (42.1)	15/76 (19.7)	19.2 (5.1, 33.3)
Week 26	24/77 (31.2)	22/76 (28.9)	11/76 (14.5)	16.7 (3.7, 29.7)

Source: Table 14.2-1, pp.199-200 of the HURON clinical study report

6.10 The PBAC noted the proportion of patients whose vitreous haze score decreased to 0 at week 8 (primary outcome nominated in submission) was statistically significantly higher in the dexamethasone implant arm compared with sham. The PBAC noted the treatment effect began to reduce from week 12–16.

6.11 The mean improvement in best corrected visual acuity from baseline to week 26 is summarised in Figure 1.

**Figure 1: Mean improvement in best corrected visual acuity from baseline to week 26 of the HURON trial**



Source: Figure 2-5, p.58 of the submission

- 6.12 The PBAC noted that the mean improvement in best corrected visual acuity from baseline was significantly greater in the dexamethasone implant groups than in the sham group.
- 6.13 There were statistically significant differences in mean improvement in quality of life measures (measured by the Visual Function Questionnaire-25 (VFQ-25)) from baseline between dexamethasone and sham. However there was no statistically significant difference between groups in the raw composite score. The ESC noted that the difference in improvement was driven by a statistically significant difference between the treatment groups at baseline.
- 6.14 The indirect comparison between dexamethasone implant (HURON) and intravitreal triamcinolone acetonide (Shin et al., 2015) for reduction in central retinal thickness showed no statistically significant difference between treatments. However, these results should be interpreted with caution, as there was significant heterogeneity between trials (population, methodology) and wide confidence intervals.
- 6.15 The indirect comparison between dexamethasone implant (HURON) and adalimumab (VISUAL I) showed no statistically significant difference between the two treatments in terms of efficacy. However these trials were conducted in different populations and the results should be interpreted with caution.

### **Comparative harms**

- 6.16 Treatment with dexamethasone implant (700 µg or 350 µg) was associated with a similar overall incidence of adverse events compared to sham. The most frequently reported events in the HURON trial were increased intraocular pressure, conjunctival haemorrhage, eye pain, iridocyclitis, uveitis, ocular discomfort, cataract, macular oedema and ocular hypertension. The PBAC noted that treatment with dexamethasone implant was generally associated with a higher rate of increased intraocular pressure, cataract, conjunctival haemorrhage, ocular discomfort and ocular hypertension than sham treatment.
- 6.17 Based on an expanded assessment of harms, important identified risks associated with dexamethasone implant include glaucoma, ocular hypertension, increased intraocular pressure, cataract formation, vitreous haemorrhage/detachment, device dislocation and implant misplacement.
- 6.18 There is limited safety data available for more than one administration of dexamethasone implant for posterior segment uveitis. The ESC noted the PSCR (p5) stated there are longer term data from 12 observational studies including nine studies with multiple (up to six) implants. The PSCR (p5) claimed the studies consistently demonstrate that repeat use of dexamethasone is both safe and effective and consistent with those observed after initial administration of dexamethasone implant in the HURON trial. The PBAC considered that there were no significant safety concerns for dexamethasone implant evident for use in this condition. In addition, the PBAC considered that the ocular adverse events reported for dexamethasone implant are likely to be similar to those reported for intravitreal triamcinolone.

## Benefits and harms

6.19 A summary of the comparative benefits and harms for dexamethasone implant versus sham is presented in Table 5 below.

**Table 5: Summary of comparative benefits and harms for dexamethasone implant 700 µg and sham**

<b>Benefits</b>				
<b>Event</b>	<b>Dexamethasone</b>	<b>Sham</b>	<b>Difference</b>	
Patients who achieved a vitreous haze score of 0 at week 8, n/N (%)	36/77 (46.8)	9/76 (11.8)	27 (35%)	
Mean number of letters gained BCVA from baseline to week 26 (letters)	10.5	3.0	7.5 (95% CI: 2.7, 12.3)	
<b>Harms</b>				
<b>Event</b>	<b>Dexamethasone</b>	<b>Sham</b>	<b>RR (95% CI)</b>	<b>RD (95% CI)</b>
Intraocular pressure increased <sup>a</sup>	17 (22.4%)	3 (4.0%)	5.59 (1.71, 18.29)	0.18 (0.08, 0.29)
Conjunctival haemorrhage <sup>a</sup>	19 (25.0%)	10 (13.3%)	1.88 (0.93, 3.76)	0.12 (-0.01, 0.24)
Cataract <sup>a</sup>	8 (10.5%)	2 (2.7%)	3.95 (0.87, 17.98)	0.08 (0.00, 0.16)
Ocular hypertension <sup>a</sup>	5 (6.6%)	0 (0.0%)	9.87 (0.55, 177.49)	0.07 (0.01, 0.13)

Source: Table 14.2-1, pp.199-200 of the HURON clinical study report; Figure 2-5, p.58 of the submission; Table 2-18, p.74 of the submission.

Abbreviations: HR, hazard ratio; BCVA, best corrected visual acuity

<sup>a</sup> Based on 26 week trial period

6.20 On the basis of the direct evidence presented in the submission, for every 100 patients treated with dexamethasone implant compared with no treatment there would be an additional 35 patients whose visual haze changes from cloudy to clear over 8 weeks.

6.21 Patients treated with dexamethasone implant would have a greater improvement in visual acuity compared with no treatment, with the average patient gaining an additional 7.5 letters on a standard eye chart.

6.22 On the basis of the direct evidence presented in the submission, for every 100 patients treated with dexamethasone implant compared to no treatment there would be over a period of 26 weeks:

- Approximately 18 additional patients with increased intraocular pressure;
- Approximately 12 additional patients with conjunctival haemorrhage;
- Approximately 8 additional patients with cataract;
- Approximately 7 additional patients with ocular hypertension.

## Interpretation of clinical evidence

6.23 The submission described dexamethasone implant as superior in terms of efficacy compared with sham, and inferior in terms of safety compared with sham but with a manageable safety profile.

- 6.24 The effectiveness of dexamethasone implant over current standard of care (periocular, intravitreal or systemic corticosteroids) has not been established. In the HURON trial, efficacy was established over sham (placebo). Despite this, the PBAC considered that sham was an appropriate proxy for standard of care as there are currently no approved or reimbursed local therapies.
- 6.25 Patients who received rescue medications (including oral or intravitreal corticosteroids) during the study had all efficacy end points set as missing for visits after the rescue medication, and values imputed using last observation carried forward (LOCF). By not allowing response to rescue medications in the trial there is no direct comparative data to inform the model of the relative efficacy and safety of dexamethasone implant to rescue medications. Due to higher use of rescue medications in the sham arm throughout the trial, this biased the analysis against sham. The PSCR (p4) agreed that efficacy estimates from the HURON trial did not capture the efficacy of rescue medication however, argued that the use of LOCF for all treatment visits after initiation of rescue medication was a reasonable statistical method to address this. The ESC noted that LOCF may be used when data is missing at random, however in this case missing data is not random, since greater numbers of sham patients would be expected to receive rescue medicines. The ESC considered that imputation using LOCF in this case is likely to favour dexamethasone. The pre-PBAC response (p4) strongly disagreed with the ESC and argued that the application of a LOCF procedure was appropriate and could be considered conservative given that spontaneous resolution of posterior segment uveitis was highly unlikely in the absence of treatment with further deterioration in a patient's outcomes likely. The PBAC noted that the analysis did not incorporate the efficacy of rescue medications and considered that this approach may not be reflective of current clinical practice. However, the PBAC considered that a clinically meaningful treatment effect in favour of dexamethasone implant was indicated by the lower proportion of patients who required rescue medicines in the dexamethasone 700 µg arm compared to sham (Table 6).

**Table 6: Proportion of patients requiring rescue medication in the HURON trial (ITT)**

From baseline to study visit	Patient requiring rescue medication, n/N (%)			Dexamethasone 700 µg implant vs. sham p-value
	Dexamethasone implant 700 µg (n=77)	Dexamethasone implant 350 µg (n=76)	Sham (n=76)	
Week 3	1/77 (1.3)	2/76 (2.6)	11/76 (14.5)	0.002
Week 6	4/77 (5.2)	3/76 (3.9)	14/76 (18.4)	0.011
Week 8	6/77 (7.8)	4/76 (5.3)	17/76 (22.4)	0.012
Week 12	11/77 (14.3)	6/76 (7.9)	22/76 (28.9)	0.027
Week 16	15/77 (19.5)	10/76 (13.2)	25/76 (32.9)	0.059
Week 20	15/77 (19.5)	14/76 (18.4)	27/76 (35.5)	0.026
Week 26	17/77 (22.1)	19/76 (25.0)	29/76 (38.2)	0.030

Source: Table 14.2-12, p.224 of HURON clinical study report  
Abbreviations: ITT, intention-to-treat

- 6.26 The PBAC noted there are limited long-term data around efficacy, safety and timing of repeat dexamethasone implants. However, while some attenuation of response

may be seen with repeat implants, the PBAC considered it was not unreasonable to expect that repeat implants in individuals with a prior satisfactory response would have efficacy.

- 6.27 The PBAC considered that the claim of superior comparative effectiveness to sham was reasonable.
- 6.28 The PBAC considered that the claim of inferior comparative safety between dexamethasone and sham was reasonable.
- 6.29 The submission described dexamethasone as not statistically significantly different from intravitreal triamcinolone acetonide for efficacy or safety. The PBAC considered that limited conclusions could be drawn from the indirect comparison due to significant heterogeneity between trials. The PBAC considered it likely that the ocular adverse events reported with dexamethasone implant would be similar to those reported for intravitreal triamcinolone acetonide.
- 6.30 The submission described dexamethasone implant as non-inferior in terms of effectiveness compared with adalimumab, with a different safety profile. The PBAC considered these claims were inadequately supported by the available data.

### **Economic analysis**

- 6.31 The submission presented a modelled cost-utility analysis comparing dexamethasone implant to sham in patients with non-infectious posterior segment uveitis.

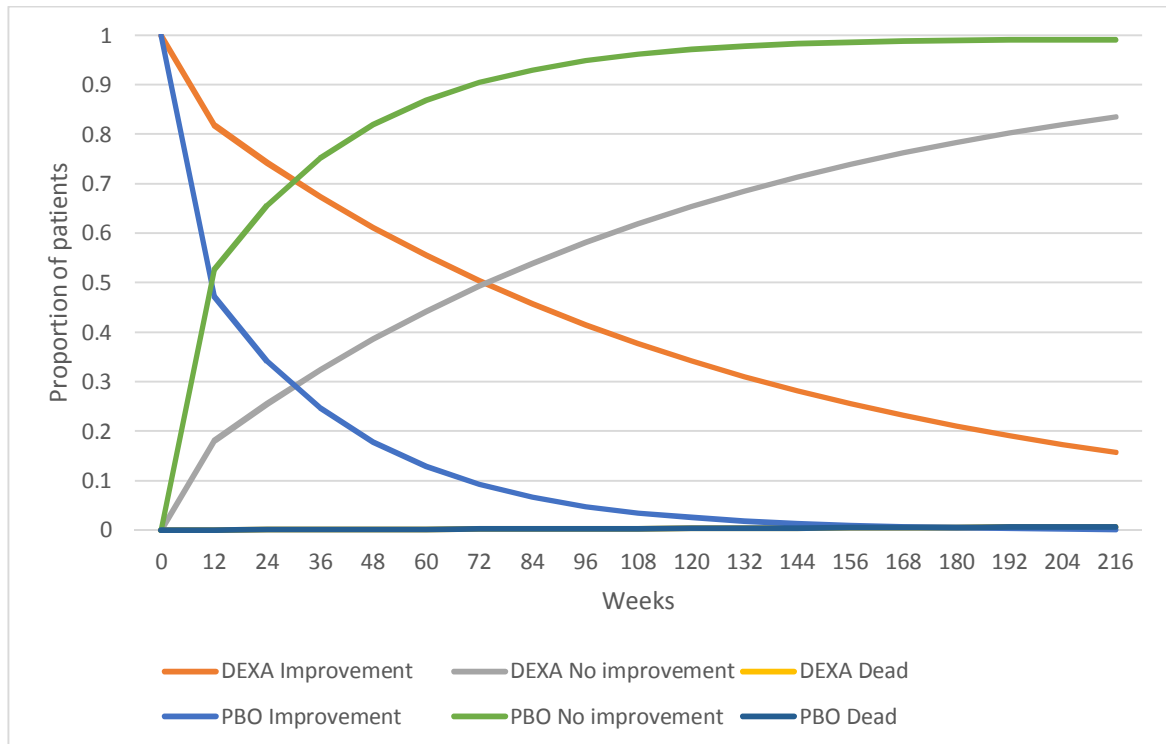
**Table 7: Summary of model structure and rationale**

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Proportion of patients with improvement in best corrected visual acuity Quality-adjusted life years
Time horizon	Four years in the model base case (1-8 years in sensitivity analysis) Six months in trial-based analysis, consistent with HURON trial length
Methods used to generate results	Markov analysis
Health states	Two treatment arms are modelled: treatment with dexamethasone implant, and current standard of care (placebo). The modelled health states are defined by whether a patient experiences an improvement in best corrected visual acuity compared to baseline: <ul style="list-style-type: none"> <li>• Baseline health state</li> <li>• Improvement in best corrected visual acuity compared with baseline (defined as <math>\geq 5</math> letter gain in BCVA in base case)</li> <li>• No improvement in best corrected visual acuity compared with baseline health state</li> <li>• Death</li> </ul>
Cycle length	12 weeks
Transition probabilities	Key transition probabilities were derived from HURON trial: <ul style="list-style-type: none"> <li>• probability of improvement (achievement of <math>\geq 5</math> letter gain in BCVA in base case)</li> <li>• probability of uveitis relapse</li> <li>• probability of retreatment with subsequent dexamethasone implant</li> <li>• probability of regaining improvement with subsequent implant</li> <li>• probability of death (ABS life tables)</li> </ul>
Software package	TreeAge Pro with bilinks to Excel

Source: Table 3-1, p.95 of the submission

6.32 The model structure does not accurately reflect the relapsing inflammatory nature of the condition or account for the natural resolution of symptoms or the impact of rescue medications. Patients with no improvement in the initial cycle can only remain in this state or die (Figure 2). The PSCR (p5) argued that spontaneous resolution of posterior segment uveitis is highly unlikely in the absence of treatment. The ESC agreed with the PSCR but considered that it was problematic that patients who enter the 'no improvement' health state can only remain in this state or die each cycle. The ESC considered this may not be representative of current clinical practice, where patients would be treated with alternative therapies also likely to impact upon visual acuity and experience subsequent episodes of relapse. The pre-PBAC response (p2) stated that a conservative model was presented given it does not allow patients to experience deterioration of visual acuity beyond that observed at baseline and the costs and detrimental effects associated with blindness in the future are not included. The PBAC agreed with the ESC that the transitions in the model for patients with no improvement in the initial cycle was a source of uncertainty.

**Figure 2: Markov trace of the proportion of patients in health states by treatment group (dexamethasone implant versus sham) for improvement defined by  $\geq 5$  letter increase in best corrected visual acuity**



Source: Figure 3.7.1 of Commentary, p64. Constructed during the evaluation using TreeAge model 'Model – dexamethasone implant vs sham' presented with the submission.

6.33 The ESC noted that although the economic model incorporated the costs of rescue medication use from the HURON trial, the efficacy associated with these treatments was not captured given the censoring of data at the point of rescue therapy being required. The PSCR (p5) accepted that if costs for rescue medications are included in the model then the impact of rescue treatments should be incorporated. The PSCR (p7) provided a revised analysis removing these costs. The ESC noted this increased the base case ICER from QALY\$15,000/QALY - \$45,000/QALY gained to QALY\$45,000/QALY - \$75,000/QALY gained. The ESC considered the removal of costs was appropriate given the benefits of alternative treatments were not captured. However, the ESC also noted that the model may not adequately capture standard care due to the absence of outcome data post rescue medicines. The pre-PBAC response (p1) stated that evidence comparing a full management algorithm with and without dexamethasone is not available and is unlikely to ever become available given that posterior segment uveitis is a rare condition. To address remaining uncertainties in the model the pre-PBAC response (p3) provided a revised analysis which included a ██████% rebate of government expenditure on dexamethasone implant when used to treat posterior segment uveitis. The PBAC noted this reduced the base case ICER to \$15,000/QALY - \$45,000/QALY gained.

6.34 Change in visual acuity was the sole outcome used to model the disease course which may not best represent the relapsing inflammatory nature of the condition, although it may be the most patient relevant measure. The PBAC noted that increases in BCVA of  $\geq 5$  to  $\geq 15$  letters have been considered clinically important and the submission presented ICERs based on an improvement in  $\geq 5$ ,  $\geq 10$  and  $\geq 15$  letters. The ESC noted the differences in ICER for the base case (improvement of  $\geq 5$

letters), improvement of  $\geq 10$  letters and improvement of  $\geq 15$  were between \$15,000/QALY - \$45,000/QALY and \$45,000/QALY - \$75,000/QALY (Table 8). The revised base case analysis presented in the pre-PBAC response updated these ICERs to \$15,000/QALY - \$45,000/QALY gained (improvement of  $\geq 5$  letters), \$15,000/QALY - \$45,000/QALY gained (improvement of  $\geq 10$  letters) and \$15,000/QALY - \$45,000/QALY gained (improvement of  $\geq 15$  letters). The PBAC considered the revised ICERs were acceptable across the three outcomes and noted that the comparison of the three outcomes was informative.

- 6.35 The model has separate arms according to whether the patient receives bilateral or unilateral treatment and whether the patient's better seeing eye or worse seeing eye is treated. This is important in estimating outcomes, given the visual acuity in the better seeing eye is more representative of quality of life than the visual acuity in the worse seeing eye. As a result, treatment of the better seeing eye is generally associated with greater utility gains than treatment of the worse seeing eye. The PBAC considered that this was appropriate.
- 6.36 Key issues with the economic model are summarised in Table 8.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Transitions in the model	Patients were only able to transition to the improvement state in the initial cycle of the model (patients in the improvement state can relapse and be retreated and re-enter the improvement state). Patients who have no improvement in the initial cycle of the model remain in that state for the duration of the model, or until death.	High, favours dexamethasone
Model structure	The model uses changes in visual acuity to define health states. The use of change in visual acuity as the sole outcome to model the disease course may not best represent the relapsing inflammatory nature of the condition. Further, the base case uses a gain of $\geq 5$ letters in visual acuity to define improvement however the PBAC has indicated a preference for more stringent criteria based on $\geq 10$ -15 letter improvement. Patients in the standard care arm could not receive treatment for uveitis relapse, which is not representative of clinical practice.	Unclear
Cost of rescue medicines	A higher proportion of patients in the sham arm of the HURON trial, which directly informs the model, received rescue medication compared to the dexamethasone implant arm. The model includes the costs of rescue medicines used in the HURON trial, but the outcomes for patients who received rescue medication were not included (efficacy outcomes were treated as missing data subsequent to administration of rescue medication).	Moderate, favours dexamethasone
Extrapolation	The model extrapolates the results of a single dexamethasone implant from the HURON trial (over 26 weeks) to a four year time horizon. Patients in the improvement state in the dexamethasone treatment arm may relapse and be retreated with a dexamethasone implant each 12-week cycle. The extrapolation of these results was highly uncertain, primarily due to limited data supporting the duration of treatment effects as well as limited data on the use of repeat implants.	Unclear.
Utilities	Utility estimates which were based on mapping quality of life estimates captured in the trial to utilities based on a time trade-off. There were differences in quality of life estimates at baseline, anomalous results between improvement categories, some estimates were based on small patient numbers with high variability, and no external validation was attempted.	Unclear.
Utilities	The model included an assumption that the utility gain for patients in the standard care arm who improved was less than for patients in the dexamethasone implant arm who experienced an equivalent minimum improvement. It is likely that patients experiencing a similar minimum level of improvement would have equivalent utility gains.	Moderate; favours dexamethasone

Source: Compiled during the evaluation (see Section 3 of the submission and TreeAge model 'Model – dexamethasone implant vs sham' presented with the submission)

6.37 The extrapolation of results from the clinical trial was highly uncertain due to limited data supporting the duration of dexamethasone implant effects as well as limited data on the use of repeat implants. The PSCR (p5) argued that long term durability of dexamethasone was already accepted by PBAC in its consideration of dexamethasone implant for diabetic macular oedema. The ESC was unclear whether durability data from macular oedema would be directly relevant to uveitis which may

have a different clinical course. The pre-PBAC response (p2) stated that observational studies indicate the repeat use of dexamethasone implant is both safe and effective and that the treatment effect after repeat administration is consistent with those observed after initial administration of dexamethasone implant in the HURON trial. The PBAC considered this was acceptable as the submission was not seeking listing for maintenance treatment and given the manageable adverse event profile of dexamethasone implant.

- 6.38 The ESC considered the validity of using utility estimates (based on mapping quality of life estimates captured in the trial) to time trade-off utility values given the limitations of the data (differences between treatments at baseline, small patient numbers, anomalous results between improvement categories, no external validation). The PSCR (p5) stated that the most rigorous utilities that could have been adopted were used in the approach presented. The ESC considered this may have been the case, but the application of utilities could have been more conservative. The ESC noted that the base case used the more favourable algorithm and the utility gain for patients in the standard care arm who improved was less than for patients with dexamethasone implant who experienced the same minimum improvement. The ESC also noted that the utility derivation from the quality of life data collected in the trial was not clear. The ESC was concerned that the data appeared to generate some inconsistent results e.g. the utility gain (measured using VFQ-UI) for improvement  $\geq 10$  letters when the better seeing eye is treated being lower than the value for an improvement of  $\geq 5$  letters.
- 6.39 The model base case included an assumption that the utility gain for patients in the standard care arm who improved was less than for patients with dexamethasone implant who experienced the same minimum improvement. The submission stated that this was because the mean letters gained were greater for those in the dexamethasone treatment arm. It is likely that patients experiencing a similar minimum level of improvement would have equivalent QALY gains attached. The PSCR (p6) maintained that it was reasonable to model differential utility gains for standard care and treatment arms in the model. The PSCR (p6) argued that minimum level of improvement does not reflect the mean level of improvement and quality of life is more likely to be related to mean improvement. The PSCR (p6) noted the mean number of letters in dexamethasone improvers was higher than for improvers in the sham arm. The ESC were concerned that the utility gains for the treatment arm were potentially over counted and considered that it may have been more appropriate to define the improvement health state in a way that enabled the same utility value to be assigned regardless of treatment.
- 6.40 Treatment with dexamethasone implant was associated with the following incremental cost per QALY gained compared with sham (standard care):
- Based on the corrected economic model: \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 5$  letters in visual acuity; \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 10$  letters in visual acuity; and \$45,000/QALY - \$75,000/QALY when a definition of improvement of  $\geq 15$  letters gain in visual acuity. The results of the modelled economic evaluation base case were corrected for an error

identified during the evaluation (error in the application of probability of retreatment with dexamethasone implant).

- Based on the PSCR (p7) which presented further revised analyses that removed costs of rescue treatment from the economic model: \$45,000/QALY - \$75,000/QALY for an improvement of  $\geq 5$  letters in visual acuity; \$45,000/QALY - \$75,000/QALY for an improvement of  $\geq 10$  letters in visual acuity; and \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 15$  letters in visual acuity.
- Based on the pre-PBAC response (p3) where the costs of rescue medication are removed and a rebate of [REDACTED] % was applied: \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 5$  letters gain in visual acuity; \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 10$  letters gain in visual acuity; and \$15,000/QALY - \$45,000/QALY for an improvement of  $\geq 15$  letters gain in visual acuity.

6.41 The results of the modelled economic evaluation base case from the pre-PBAC response (p3) which included a special pricing arrangement proposal are presented in Table 9. The PBAC considered the revised ICERs in the pre-PBAC response (p3) were more acceptable and reduced the uncertainties around the cost-effectiveness of dexamethasone implant.

**Table 9: Results of the modelled economic evaluation from pre-PBAC response (p3) using the special pricing arrangement proposal**

	Dexamethasone	Standard care	Increment
<b>Base case (improvement defined as a gain of <math>\geq 5</math> letters)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.935	2.820	0.115
Incremental cost per QALY gained			\$ [REDACTED]
<b>Improvement defined as a gain of <math>\geq 10</math> letters</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.927	2.833	0.095
Incremental cost per QALY gained			\$ [REDACTED]
<b>Improvement defined as a gain of <math>\geq 15</math> letters</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.897	2.816	0.081
Incremental cost per QALY gained			\$ [REDACTED]

Source: constructed during the evaluation using TreeAge model 'Model – dexamethasone implant vs sham' presented with the submission.

6.42 The results of key sensitivity analyses, corrected for the error identified in the model, are summarised in Table 10 below.

Table 10: Results of univariate sensitivity analyses

	Incremental cost	Incremental QALYs	ICER
Base case	██████	0.115	██████
<b>Rescue medication (base case: costs, but not outcomes included)</b>			
- cost of rescue medication removed	██████	0.115	██████
<b>Time horizon (base case 4 years)</b>			
- 1 year	██████	0.048	██████
- 8 years	██████	0.132	██████
<b>Source of utilities (base case VFQ-UI)</b>			
- Scharr algorithm	██████	0.094	██████
<b>WSE utility gain for improvers (base case differs by treatment)</b>			
- WSE utility gain for improvers same for dexamethasone and placebo (VFQ-UI)	██████	0.069	██████
- WSE utility gain for improvers same for dexamethasone and placebo (SchARR algorithm)	██████	0.054	██████
<b>Threshold for relapse (base case loss of ≥ 5 letters)</b>			
- loss of ≥ 10 letters	██████	0.124	██████
- loss of ≥ 15 letters	██████	0.155	██████
<b>Retreatment if relapse (base case 95%)</b>			
- 90%	██████	0.103	██████
- 100%	██████	0.130	██████
<b>Improvement if relapse and retreatment (base case 81.8%)</b>			
- 70%	██████	0.085	██████
- 100%	██████	0.197	██████
<b>Baseline utilities equal for patients with better or worse seeing eye treated (base case differs by treated eye)</b>			
- Utilities derived from VFQ-UI	██████	0.115	██████
- Utilities derived from SchARR algorithm	██████	0.094	██████
<b>Proportion of unilateral patients (base case assumed 95.2% unilateral)</b>			
- 100% unilateral	██████	0.115	██████
- 0% unilateral (100% bilateral)	██████	0.115	██████

Source: constructed during the evaluation using TreeAge model 'Model – dexamethasone implant vs sham' presented with the submission. WSE: worse seeing eye

6.43 The redacted table shows ICERs in the range of less than \$15,000/QALY to \$105,000/QALY. The economic model is sensitive to the costs of rescue medication, the time horizon, the assumption that the utility gain in patients who have their worse seeing eye treated differs by treatment type, threshold for relapse and the proportion of unilateral patients. The PBAC considered the ICERs derived from the sensitivity analyses fell within an acceptable range to be considered cost-effective. The PBAC considered the uncertainty around the cost-effectiveness of dexamethasone implant compared to standard care was adequately addressed by the proposed rebate.

**Drug cost/patient/year: \$ [REDACTED]**

6.44 The estimated annual cost for dexamethasone implant was \$ [REDACTED]. This was also based on 2.22 implants per year (generated by running the corrected economic model with a time horizon of 1 year) at a proposed dispensed price of \$ [REDACTED], which does not include the rebate of [REDACTED]% proposed in the pre-PBAC response (p3). The cost for delivery of the intravitreal implant of the device is \$300.75 (MBS item 42740).

**Estimated PBS usage & financial implications**

6.45 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with PBS listing of dexamethasone implant for the treatment of non-infectious posterior segment uveitis over the first six years of listing. The ESC noted the PSCR (p7) provided revised financial estimates which used incidence and prevalence data from Colby et al., 2017 and reduced estimated uptake rates. The original submission included an incidence of 3.25:100,000, prevalence of 11.55:100,000 and uptake in Years 1-6 to be 10-34%. The revised values from the PSCR include incidence of 13:100,000, prevalence of 22:100,000 and uptake in Years 1-6 of 5-7%. The PBAC considered the use of the revised incidence and prevalence data appropriate. The pre-PBAC response (p3) provided revised financial estimates to incorporate the special pricing arrangement to rebate [REDACTED]% of government expenditure which is included Table 11.

**Table 11: Estimated utilisation and cost to the PBS in the first six years of listing**

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Australian adult population	██████	██████	██████	██████	██████	██████
Prevalence of uveitis affected posterior segment (11.55 per 100,000 persons)	██████	██████	██████	██████	██████	██████
Incidence of uveitis affected posterior segment (3.25 per 100,000 persons)	██████	██████	██████	██████	██████	██████
Total population (prevalent + incident)	██████	██████	██████	██████	██████	██████
Proportion with non-infectious origin (83.1%)	██████	██████	██████	██████	██████	██████
Proportion with vision loss (90%)	██████	██████	██████	██████	██████	██████
Expected uptake rate	10%	14%	20%	25%	31%	34%
<b>Treated patient population</b>	██████	██████	██████	██████	██████	██████
Estimated implants (2.03 per patient)	██████	██████	██████	██████	██████	██████
Total cost (\$██████ DPMQ per implant)	██████	██████	██████	██████	██████	██████
Patient co-payments (\$16.26 per implant)	██████	██████	██████	██████	██████	██████
Cost of anti-glaucoma medications (28.6% of patients, 12 scripts per patient, \$19.01 per script)	██████	██████	██████	██████	██████	██████
<b>Net cost to the PBS/RPBS</b>	██████	██████	██████	██████	██████	██████
Administration cost (\$255.65 per implant)	██████	██████	██████	██████	██████	██████
Additional monitoring costs (4 visits per implant, \$36.55 per visit)	██████	██████	██████	██████	██████	██████
<b>Total cost to Australian government<sup>a</sup></b>	██████	██████	██████	██████	██████	██████
<b>Net cost to the PBS/RPBS (revised in PSCR)</b>	██████	██████	██████	██████	██████	██████
<b>Net cost to the PBS/RPBS (revised in pre-PBAC response)<sup>b</sup></b>	██████	██████	██████	██████	██████	██████
<b>Total cost to Australian government (using revised PSCR net cost to PBS/RPBS)</b>	██████	██████	██████	██████	██████	██████
<b>Total cost to Australian government (revised in pre-PBAC response)<sup>b</sup></b>	██████	██████	██████	██████	██████	██████

Abbreviations: DPMQ, dispensed price per maximum quantity; PBS, Pharmaceutical Benefits Scheme; PSCR, Pre-Sub-Committee Response; RPBS, Repatriation Pharmaceutical Benefits Scheme

Source: Table 4-6 (p 143), Table 4-7 (p 144), Table 4-8 (p 144), Table 4-9 (p 145), Table 4-13 (p 146), Table 4-17 (p 148), Table 4-18 (p 149), Table 4-24 (p 152), Table 4-25 (p 153), Table 4-26 (p 153), Table 4-27 (p 153) of the submission

<sup>a</sup> The estimated total cost to the Australian government incorrectly used the 100% MBS schedule fee rather than the 85% benefit value for monitoring and administration costs in the submission. These values were corrected during the evaluation.

<sup>b</sup> Costs includes special pricing arrangement proposal, revised prevalence and uptake rates from PSCR and 85% MBS schedule fees from ESC Advice.

6.46 Based on the revised financial estimates from the pre-PBAC response (p3), in year 6 the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RPBS would be less than \$10 million per year.

6.47 The PBAC noted that the estimated utilisation and financial implications were uncertain due to the following issues:

- The identification and selection of epidemiology estimates was poorly documented in the submission. Most estimates were derived from older data sources in various international settings that may not be relevant to current Australian clinical practice. The most recent Australian data identified in the submission suggested a much higher incidence and prevalence of disease compared to the estimates used in the submission. Overall, it appeared likely that the submission has underestimated the size of population affected by posterior non-infectious uveitis. The PBAC noted this had been recognised and addressed by the sponsor in the PSCR (p6) and the financial estimates updated.
- The submission may have overestimated the proportion of posterior segment non-infectious uveitis patients suitable for dexamethasone implant. Expert advice for the sponsor's advisory panel indicated that only 10-20% of patients with posterior non-infectious uveitis would be suitable for treatment with dexamethasone implant in clinical practice (although it was unclear what clinical characteristics were included in this consideration). This would reduce the financial estimates.
- The submission claimed that the estimated uptake rates were consistent with expert advice. These estimates could not be validated during the evaluation as the expert report did not appear to consider numerical uptake rates. If approved for listing, dexamethasone implant would be the first PBS listed therapy available for non-infectious posterior segment uveitis. The estimated uptake rates may be reasonable in a patient population with other existing treatment options available but are likely to be underestimates in a patient population with high clinical need for a new treatment.
- The submission estimated that patients would use 2.03 implants per year based on values derived from the economic model using a one-year time horizon. When the error in the model was corrected (error in application of probability of retreatment with dexamethasone implant), the economic model with a one-year time horizon provides an estimate of 2.22 implants per year. The PBAC considered the number of implants used in the estimates to be reasonable.

### **Quality use of medicines**

6.48 The submission indicated that the sponsor will continue to undertake pharmacovigilance and risk management activities to support the appropriate use of dexamethasone implant in clinical practice. The submission noted that existing activities are focused around diabetic macular oedema and no new activities are proposed for uveitis.

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of dexamethasone implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye where systemic therapy or further intensification of systemic therapy is not required or contraindicated.
- 7.2 The PBAC is satisfied that dexamethasone implant provides, for some patients, a significant improvement in efficacy compared with standard of care. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of dexamethasone implant would be acceptable at the price proposed in the submission.
- 7.3 The PBAC advised the restriction should be an Authority Required (Telephone) listing.
- 7.4 The PBAC accepted that there is a clinical need for dexamethasone implant as there are currently no approved or reimbursed local therapies for the treatment of non-infectious posterior segment uveitis.
- 7.5 The PBAC noted that the use of sham (placebo with the use of rescue medicines) as a proxy for standard care was the main comparator nominated in the submission based on the HURON trial. The PBAC also noted that censoring of data occurred at the point of rescue therapy being required in both arms in the trial. The PBAC considered that in clinical practice, patients will have access to a range of local corticosteroids (periocular injections or intravitreal injections) or systemic therapies to manage uveitis. As a result, the PBAC considered that the sham treatment arm in the HURON trial may not represent current true standard care for posterior segment uveitis.
- 7.6 The PBAC noted that intravitreal triamcinolone acetonide was nominated as a secondary comparator as dexamethasone may replace unregistered or off-label use of this medicine. The PBAC considered this comparator was appropriate but the indirect comparison based on the available data provided limited information due to the significant heterogeneity across the trials. The PBAC noted that adalimumab was nominated as a secondary near market comparator but considered that this comparison was not informative as dexamethasone implant and adalimumab are likely to be used in different populations with non-infectious posterior segment uveitis.
- 7.7 The PBAC considered that the claim of superior effectiveness compared with sham was reasonable as the clinical efficacy of dexamethasone implant up to 6 months was adequately demonstrated. The PBAC noted the significant improvement in vitreous haze score in patients treated with the 700 µg dexamethasone implant compared to sham, with the treatment effect starting to reduce from week 12–16. The PBAC also noted the significant mean improvement in best corrected visual acuity from baseline in the dexamethasone arm compared to the sham group and its preserved effect over the 26 weeks of the trial.
- 7.8 The PBAC was concerned that the treatment efficacy estimates did not incorporate rescue medicine use which may not be reflective of current clinical practice.

However, the PBAC considered that the HURON trial had a low risk of bias and that the lower proportion of patients who required rescue medicines in the dexamethasone 700 µg implant arm indicated that patients receiving the implant achieved a clinically meaningful treatment effect.

- 7.9 The PBAC considered that the claim of inferior safety between dexamethasone implant and sham was reasonable. The PBAC considered that there were no significant safety concerns and the likely ocular side effects that could occur while using dexamethasone implant are manageable and would be similar to those when using intravitreal triamcinolone.
- 7.10 The PBAC noted the data from observational studies indicating repeat use of dexamethasone implant is safe and effective. The PBAC considered these data were acceptable for this rare condition as the submission was not seeking a listing for maintenance treatment and given the manageable adverse event profile of dexamethasone implant.
- 7.11 The PBAC noted that in the cost-utility analysis comparing dexamethasone implant to sham, the model structure did not allow patients to transition to the improvement states after the initial 12 week cycle. The PBAC noted that in clinical practice such patients would likely be treated with alternative treatments that may impact on visual acuity. The PBAC considered this was a source of uncertainty in the model which was likely biased in favour of dexamethasone.
- 7.12 The PBAC noted that as the benefits of rescue medicines were not included in the model, the costs of these medicines should also be removed as per the revised analysis provided in the PSCR (p7). However, the PBAC considered that as a result the model may not adequately capture standard care due to the absence of outcome data post rescue medicines.
- 7.13 The PBAC noted that the pre-PBAC response (p3) provided a revised analysis which included a █████% rebate of government expenditure on dexamethasone implant when used to treat non-infectious posterior segment uveitis
- 7.14 The PBAC considered the uncertainty regarding the cost-effectiveness of dexamethasone implant compared to standard care was adequately addressed by the proposed rebate.
- 7.15 The PBAC considered the financial estimates to be reasonable with little risk of use beyond the proposed population.
- 7.16 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that dexamethasone implant should not be treated as interchangeable on an individual patient basis with any other medicine listed in the PBS.
- 7.17 The PBAC advised that dexamethasone implant is not suitable for prescribing by nurse practitioners, as it must be prescribed by an ophthalmologist.
- 7.18 The PBAC recommended that the Early Supply Rule should apply.

7.19 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DEXAMETHASONE Intravitreal injection 700 micrograms	1	0	Ozurdex®	Allergan

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Non-infectious uveitis
<b>PBS Indication:</b>	Non-infectious posterior segment uveitis
<b>Treatment phase:</b>	-
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist;  or  Must be treated in consultation with an ophthalmologist.
<b>Clinical criteria:</b>	Patient must have a documented best-corrected visual acuity (BCVA) of 6/12 or less secondary to vitreous haze or macular oedema.  AND  <i>Patient must have unilateral, asymmetric or bilateral flare-up where systemic treatment or further intensification of systemic treatment is not clinically indicated;</i>
<b>Population criteria:</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	-

## **9 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.

## **10 Sponsor's Comment**

Allergan welcomes the PBAC's decision to recommend dexamethasone implant for treatment of non-infectious uveitis affecting the posterior segment of the eye.