

## 5.04 FLUOCINOLONE ACETONIDE, Intravitreal injection 190 micrograms, Iluvien<sup>®</sup>, Specialised Therapeutics Alim Pty Ltd.

### 1 Purpose of submission

- 1.1 The submission requested an Authority Required listing for fluocinolone acetonide (FA) for the treatment of diabetic macular oedema (DMO, also referred to as DME) who are unsuitable for, contraindicated to, or have failed treatment with vascular endothelial growth factor (VEGF) inhibitors.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) versus dexamethasone (DEX) intravitreal implant, using clinical evidence from an indirect comparison.

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

Component	Description
Population	Patients with DMO who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP
Intervention	ILUVIEN (FA) 190 micrograms (µg) intravitreal implant in applicator
Comparator	Intravitreal implant containing 700 µg DEX in a solid polymer drug delivery system
Outcomes	Proportion achieving ≥ 15-letter improvement in BCVA; change from baseline in BCVA letter score; time to ≥15-letter increase from baseline in BCVA; distribution of BCVA; proportion achieving ≥ 10-letter improvement in BCVA; three-step worsening in ETDRS multi-step eye scale of diabetic retinopathy; mean change from baseline in centre point thickness; change from baseline in excess centre point thickness; mean change from baseline in macular volume (mm <sup>3</sup> ); time to ≥50% reduction from baseline in excess foveal thickness; quality of life (VFQ-25 and VFQ-39); treatment-emergent adverse events; mean change from baseline in IOP; IOP-related events; cataract-related events in phakic patients.
Clinical claim	In patients with DMO FA was no worse than DEX at improving/maintaining BCVA, with a similar safety profile

Source: Table 2, p1 of the submission.

BCVA = best corrected visual acuity; DEX = dexamethasone; DMO = diabetic macular oedema; FA= fluocinolone acetonide; IOP= intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VFQ = Vision Function Questionnaire.

### 2 Background

#### **Registration status**

- 2.1 FA was TGA registered on 29 July 2019 for the treatment of DMO in patients who have been previously treated with a course of corticosteroids (CS) and did not have a clinically significant rise in intraocular pressure (IOP).

### 3 Requested listing

- 3.1 The requested listing is provided below. Suggested additions are in italics and deletions are in strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
FLUOCINOLONE ACETONIDE flucinolone acetamide 190 microgram implant, 1	1	0	Published \$9,486.82	ILUVIEN Specialised Therapeutics Alim

<b>Category / Program:</b> 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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing Only
<b>Indication:</b> Diabetic macular oedema (DMO)
<b>Treatment Phase:</b> Initial treatment and continuing treatment
<b>Treatment criteria:</b>
Must be treated by an ophthalmologist or in consultation with an ophthalmologist
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have visual impairment due to diabetic macular oedema
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/400), in the eye proposed for treatment
<b>AND</b>
<b>Clinical criteria:</b>
The condition must be diagnosed by optical coherence tomography; or
The condition must be diagnosed by fluorescein angiography
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; or
Patient must be unsuitable for treatment with VEGF inhibitors; or
Patient must have failed prior treatment with VEGF inhibitors
<b>AND</b>
<b>Population criteria:</b>
Patient must have had a cataract removed in the treated eye; or
Patient must be scheduled for cataract surgery in the treated eye
<b>Administrative Advice:</b>
<b>Prescribing Instructions:</b>
Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. A written application must include: a) a completed authority prescription form; b) a completed Diabetic Macular Oedema (DMO) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Diabetic Macular Oedema (DMO) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.
<b>Administrative Advice:</b>
<b>Prescribing Instructions:</b>
Repeat Authorities for the same eye will not be authorised within 30 months of initial script.
<b>Prescribing Instructions:</b>
<b>Administrative Advice:</b>
Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

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<b>Administrative Advice:</b> The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>
<b>Category / Program:</b> <i>General Schedule (Code GE)</i>
<b>Prescriber type:</b> <input type="checkbox"/> <i>Dental</i> <input checked="" type="checkbox"/> <i>Medical Practitioners</i> <input type="checkbox"/> <i>Nurse practitioners</i> <input type="checkbox"/> <i>Optometrists</i> <input type="checkbox"/> <i>Midwives</i>
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> <i>Authority Required – Telephone/Electronic/Emergency</i>
<b>Indication:</b> <i>Diabetic macular oedema (DMO)</i>
<b>Treatment Phase:</b> <i>Continuing treatment</i>
<b>Treatment criteria:</b> <i>Must be treated by an ophthalmologist or in consultation with an ophthalmologist</i>
<b>AND</b>
<b>Clinical criteria:</b> <i>Patient must have previously been issued with an authority prescription for this drug for the same eye</i>
<b>Prescribing Instructions:</b> <i>The treatment must not be administered within 30 months from the start of a previous course of treatment.</i>
<b>Administrative Advice:</b> <i>Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>

- 3.2 The ESC noted the restriction did not require patients to have been previously treated with a CS and considered this would mean that a broader population was proposed for PBS listing than the TGA registration.
- 3.3 In contrast to DEX and the VEGF inhibitors the proposed PBS listing did not specify that treatment must be monotherapy (or in combination with laser photocoagulation), and the treatment must be the sole PBS-listed therapy for the condition. This would allow concomitant treatment with other PBS-listed DMO therapies. The PBAC agreed with the PSCR that it would not be clinically appropriate to preclude patients from receiving concomitant therapies for the entire three-year duration of FA.
- 3.4 The Prescribing Instruction that ‘repeat authorities for the same eye will not be authorised within 30 months of initial script’ is not consistent with the Product Information, which allows for retreatment after 12 months. The ESC considered that retreatment should not occur within 36 months and this should be stipulated within the restriction.
- 3.5 The proposed initial listing criteria required a best corrected visual acuity score (BCVA) of between 78 and 20. The current DEX and VEGF inhibitor criteria requires a BCVA of between 78 and 39 letters to access initial treatment. Lowering the BCVA threshold for FA (to 20) would result in patients with poorer visual acuity being eligible for treatment compared to the current listings. While the FAME study included patients with this degree of loss of visual acuity, the cost-effectiveness of treating patients with poorer visual acuity (BCVA 20-39 letters) has not been demonstrated. The ESC noted that the additional patient population with BCVA 20-39 letters was likely to be small, and that, on balance, the listing criteria was not inappropriate.

- 3.6 Consistent with the DEX criteria, patients are required to have had a cataract removed in the treated eye (i.e. have a pseudophakic lens) or be scheduled for cataract surgery in the treated eye.
- 3.7 The submission did not request a special pricing arrangement (SPA) for FA but noted that DEX (the comparator) has a SPA.

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

## 4 Population and disease

- 4.1 DMO is a complication of diabetes and occurs when leakage of fluid from small retinal blood vessels affects the macula leading to retinal thickening or hard exudates within one disc diameter of the centre of the macula. The pathophysiology of macular oedema is likely to be multifactorial. Contributing features may include increased leakage of fluid due to a break down in the blood retinal barrier, reduced osmotic pressure, increased intravascular fluid load, increased arterial perfusion pressure, tissue hypoxia and raised VEGF. Once DMO has developed, treatment is needed to stop/slow the progression of the disease and maintain visual acuity. Untreated, DMO causes blurring and distortion of central vision, measured as a reduction in BCVA measured according to the method used in the Early Treatment Diabetic Retinopathy Study (ETDRS).
- 4.2 The VEGF inhibitors (aflibercept, ranibizumab, bevacizumab) are considered first-line therapies for DMO with a 'treat and extend' approach generally adopted (i.e. extending the time period between injections, based on response) (European Society of Retina Specialists, EURETINA<sup>1</sup>). Corticosteroid implants are generally used as second-line treatments but may be appropriate as a first-line treatment option in patients with a history of major cardiovascular events or in those patients for whom monthly injections are not possible, noting that the 'treat and extend' approach can decrease this injection frequency. Intraocular pressure (IOP) needs to be closely monitored in all patients and pseudophakic patients are preferred for CS treatment due to the high risk of cataract surgery<sup>1</sup>.
- 4.3 The corticosteroid FA is a non-biodegradable intravitreal implant containing 190 micrograms of FA, releasing approximately 0.2 micrograms/day for approximately 36 months. Corticosteroids inhibit a range of inflammatory responses (including oedema) and have been shown to reduce levels of VEGF (FA Product Information).
- 4.4 The ESC noted that, as a non-biodegradable implant, removal was sometimes necessary and that dissociation has been seen with FA implants in general (Nicholson et al<sup>2</sup>) and with ILUVIEN<sup>®</sup> in particular (post-marketing reports of device dislocation [implant migration]<sup>3</sup>). Potential intra-ocular adverse events could arise as a result of

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<sup>1</sup> Guidelines for the Management of Diabetic Macular Oedema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2017; 237: 185-222

<sup>2</sup> Nicholson BP et al. Evaluation of fluocinolone acetonide sustained release implant dissociation during implant removal and exchange surgery. *Am J Ophthalmol* 2012; 154(6): 969-973.

<sup>3</sup> ILUVIEN Product Information, Section 4.8 Adverse effects (Undesirable effects).

the removal or attempted removal. The pre-PBAC response stated Nicholson et al referred to a different formulation of fluocinolone acetonide (Retisert®). Retisert implants (5 mm x 3 mm x 2 mm) are considerably larger than Iluvien implants (3.5 mm long x 0.37 mm in diameter), and in vitro stability studies show that the strength of the adhesive bond between the silicone cup reservoir and the suture tab is reduced with prolonged hydration, indicating a potential for the separation of these components. The Sponsor stated that this is not the case for Iluvien.

## 5 Comparator

- 5.1 The submission nominated DEX as it is currently PBS listed for the treatment of DMO in patients who have a contraindication, have failed or are unsuitable for VEGF inhibitors. The ESC noted DEX was recommended on the basis that it had inferior effectiveness and safety compared to aflibercept and ranibizumab (paragraph 7.1, DEX Public Summary Document (PSD), March 2016 PBAC meeting) and a lower price (compared to the VEGF inhibitors) was required in view of this efficacy and safety inferiority (paragraph 6.35, DEX PSD, March 2016 PBAC meeting).

*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 hearing**

- 6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

- 6.3 No randomised controlled trials comparing FA implants with DEX implants were identified. Therefore, the submission was based on an indirect comparison of four randomised trials: a pooled analysis of two identical trials comparing FA to sham injection (FAME-001a and FAME-001b) and a pooled analysis of two identical trials comparing DEX to sham injection (MEAD-010 and MEAD-011).

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

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

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
FAME 001a/ FAME 001b	Iluvien® (fluocinolone acetonide intravitreal insert), 0.18 mg Protocol No. C-01-05-001A. A randomized, double-masked, parallel group, multi-centre, dose-finding comparison of the safety and efficacy of ASI-001A 0.5 µg/day and ASI-001B 0.2 µg/day fluocinolone acetonide intravitreal inserts to sham injection in patients with diabetic macular oedema	Clinical study report - C-01-05-001A
	Iluvien® (fluocinolone acetonide intravitreal insert), 0.18 mg	Clinical study report - C-01-05-001B

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Trial ID	Protocol title/ Publication title	Publication citation
	Protocol No. C-01-05-001B A randomized, double-masked, parallel group, multi-centre, dose-finding comparison of the safety and efficacy of ASI-001A 0.5 µg/day and ASI-001B 0.2 µg/day fluocinolone acetonide intravitreal inserts to sham injection in patients with diabetic macular oedema	
	Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, Garretson B, Gupta A, Hariprasad SM, Bailey C, Reichel E, Soubrane G, Kapik B, Billman K, Kane FE, and Green K. Sustained Delivery Fluocinolone Acetonide Vitreous Inserts Provide Benefit for at Least 3 Years in Patients with Diabetic Macular Oedema.	Ophthalmology. 2012 119(10):2125-32
	Cunha-Vaz J, Ashton P, Iezzi R, Campochiaro P, Dugel PU, Holz FG, Weber M, Danis RP, Kuppermann BD, Bailey C, Billman K, Kapik B, Kane F, and Green K. Sustained Delivery Fluocinolone Acetonide Vitreous Implants.	Ophthalmology. 2014.121(10)1892-1903.e3
	Parrish RK 2nd, Traverso CE, Green K, Danis RP, FAME Study Group. Quantitative Assessment of Optic Nerve Changes in Patients With Diabetic Macular Oedema Treated With Fluocinolone Acetonide Vitreous Implants.	Ophthalmic Surgery, Lasers & Imaging Retina. 2016. 47(5):418-25.
	Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, Tolentino M, Gupta A, Duarte L, Madreperla S, Gonder J, Kapik B, Billman K, Kane FE, FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular oedema.	Ophthalmology. 2011. 118(4):626-635.e2.
	Iluvien® (fluocinolone acetonide intravitreal insert), 0.18 mg Protocol No. C-01-11-008 An Open Label, Multi-Centre Extension Study Of The Safety And Utility Of The New Inserter Of Iluvien® (Fluocinolone Acetonide Intravitreal Insert) 0.19 Mg And The Safety Of Iluvien In Patients With Diabetic Macular Oedema.	FAME™ EXTENSION STUDY: Final Study Report. 2014
	Yang Y, Bailey C, Holz FG, Eter N, Weber M, Baker C, Kiss S, Menchini U, Ruiz Moreno JM, Dugel P, Lotery A, FAME study group. Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants.	Eye. 2015. 29(9):1173-80.
	Wykoff CC, Chakravarthy U, Campochiaro PA, Bailey C, Green K, Cunha-Vaz J. Long-term Effects of Intravitreal 0.19 mg Fluocinolone Acetonide Implant on Progression and Regression of Diabetic Retinopathy.	Ophthalmology. 2017. 124(4):440-449.
	Pearson P, Baker CW, Elliott D, Ip MS, Morse LS, Callanan D. Fluocinolone Acetonide Intravitreal Implant in Patients with Diabetic Macular Oedema: 12 Month Results IOVS.	ARVO E-abstract 4288p. 2003.
	FAME Study Group Parrish RK 2nd, Campochiaro PA, Pearson PA, Green K, Traverso CE. Characterization of Intraocular Pressure Increases and Management Strategies Following Treatment	Ophthalmic Surgery, Lasers & Imaging Retina. 2016. 47(5):426-35.

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Trial ID	Protocol title/ Publication title	Publication citation
	With Fluocinolone Acetonide Intravitreal Implants in the FAME Trials.	
Dexamethasone trials		
MEAD-010/ MEAD-011 <sup>a</sup>	Study 206207-010: A 3-year, phase 3, multicentre, masked, randomized, sham-controlled trial to assess the safety and efficacy of 700µg and 350µg dexamethasone posterior segment drug delivery system (DEX PS DDS) applicator system in the treatment of patients with diabetic macular oedema.	CSR - 206207-010 ( <i>not available and not provided by the submission</i> )
	Study 206207-011: A 3-year, phase 3, multicentre, masked, randomized, sham-controlled trial to assess the safety and efficacy of 700µg and 350µg dexamethasone posterior segment drug delivery system (DEX PS DDS) applicator system in the treatment of patients with diabetic macular oedema	CSR - 206207-011 ( <i>not available and not provided by the submission</i> )
	Mitchell P. Ozurdex mead study subgroup analysis: Dexamethasone intravitreal implant (DEX) in previously treated patients with diabetic macular oedema (DMO).	Clinical and Experimental Ophthalmology. Conference: 47th Annual Scientific Congress of the Royal Australian and New Zealand College of Ophthalmologists, RANZCO 2015. New Zealand. 43 (Supplement 1) (pp 24-25), 2015. Date of Publication: October 2015.
	Danis RP, Sadda SR, Cui H, Li X-Y, Hashad Y, Whitcup SM. Anatomic outcomes with dexamethasone intravitreal implant in diabetic macular oedema: A pooled analysis of two randomized phase 3 trials.	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. United States. 55 (13, pp 5051, 2014. Date of Publication: April 2014.
	Yoon YH, Boyer DS, Belfort R, Bandello F, Maturi RK, Augustin AJ, Li X-Y, Cui H, Hashad Y, Whitcup SM. Long-term efficacy and safety of dexamethasone intravitreal implant in phakic and pseudophakic eyes with diabetic macular oedema.	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. United States. 55 (13 pp 1779), 2014. Date of Publication: April 2014.
	Danis RP, Sadda S, Jiao J, Li XY, Whitcup SM. Relationship between retinal thickness and visual acuity in eyes with retinal vein occlusion treated with dexamethasone implant.	Retina. 2016. 36(6):1170-6.
	Danis RP, Sadda S, Li XY, Cui H, Hashad Y, Whitcup SM. Anatomical effects of dexamethasone intravitreal implant in diabetic macular oedema: a pooled analysis of 3-year phase III trials.	British Journal of Ophthalmology. 2016. 100(6):796-801.
	Maturi RK, Pollack A, Uy HS, Varano M, Gomes AM, Li XY, Cui H, Lou J, Hashad Y, Whitcup SM, Ozurdex MEAD Study Group. Intraocular pressure in patients with diabetic macular oedema treated with dexamethasone intravitreal implant in the 3-year MEAD study.	Retina. 2016. 36(6):1143-52.
	Augustin AJ, Kuppermann BD, Lanzetta P, Loewenstein A, Li XY, Cui H, Hashad Y, Whitcup SM, Ozurdex MEAD Study Group. Dexamethasone intravitreal implant in previously treated patients with diabetic macular oedema: subgroup analysis of the MEAD study.	BMC Ophthalmology. 2015. 15:150.

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Trial ID	Protocol title/ Publication title	Publication citation
	Belfort R, Boyer DS, Yoon YH, Bandello F, Maturi RK, Augustin AJ, Li X-Y, Cui H, Hashad Y, Whitcup SM. Three-year, randomized, sham controlled, phase III study of dexamethasone intravitreal implant in patients with diabetic macular oedema.	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. United States. 55 (13) (pp 1706), 2014. Date of Publication: April 2014.
	Boyer DS., Yoon YH., Belfort R. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular oedema.	Ophthalmology 2014;121(10):1904-14.

Source: Table 10, pp27-29 of the submission

<sup>a</sup> The MEAD trials were considered by PBAC when recommending DEX for DMO. Two trials previously considered (Trial 024 and BEVORDEX) were not included in this submission because they were vs ranibizumab/ bevacizumab, rather than vs sham injection.

6.5 The key features of the randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Used in economic evaluation.
<b>Fluocinolone acetate vs. sham</b>						
FAME-001a	190	R, DB, MC 36 MO	High	DMO with visual acuity of BCVA ≥19 and ≤68 letters	- Proportion achieving ≥ 15-letter improvement in BCVA (primary outcome at 24 months) -Proportion of patients ≥ 10-letter improvement in BCVA -Change from baseline in BCVA Letter Score	NA
FAME-001b	186	R, DB, MC 36 MO	High			
<b>Dexamethasone vs. sham</b>						
MEAD-010	163	R, DB, MC 36 MO	Low	DMO with visual acuity of BCVA ≥34 letters and ≤68 letters	- Proportion achieving ≥ 15-letter improvement in BCVA -Proportion of patients ≥ 10-letter improvement in BCVA -Change from baseline in BCVA Letter Score	NA
MEAD-011	188	R, DB, MC 36 MO	Low			

Source: Section 2.3, pp33-42 of the submission.

BCVA = best corrected visual acuity; DB = double blind; DMO = diabetic macular oedema; MC = multicentre; MO = months; NA = not applicable; R = randomised.

6.6 The evaluation considered the FAME studies were at risk of bias for the following reasons:

- Patients who had non-protocol therapies during the study were included in the full analysis data set;
- Approximately 30% of patients in each treatment group in the full analysis data set received at least 1 retreatment with study drug over 36 months; and
- There were six protocol amendments to the FAME trial.

6.7 The PBAC considered that the overall risk of bias in the FAME trials was likely low, as follows:

- It was appropriate for participants in the FAME studies who received non-protocol therapies (15% FA patients vs 33% sham patients) to be included in the full analysis

set, and that this had the most likely effect of masking the true effectiveness of FA.

- The protocol amendments were generally administrative and were made early in the trial and before unblinding, and were therefore unlikely to significantly bias the effect estimates.

- 6.8 Though baseline characteristics were similar across the MEAD and FAME studies, there may be transitivity issues with the indirect treatment comparison due to the heterogeneity between the trials. Data from patients who received non-protocol (concomitant) treatments in the FAME trials were included in the full analysis set, while these data were not included in the ITT analysis for the MEAD studies.
- 6.9 The key outcomes of interest included in the submission were proportion of patients achieving  $\geq 15$  letter or  $\geq 10$  letter change from baseline in BCVA at 24 and 36 months and change from baseline in BCVA score. The submission noted that the PBAC had previously indicated that “a mean BCVA change of -5 letters in the lower bound non-inferiority limit was probably reasonable” [at 12 months] when it considered the previous dexamethasone implant submission (paragraph 7.5, dexamethasone implant PSD, March 2015 PBAC meeting), although no non-inferiority margin was nominated by the submission.
- 6.10 It was noted that approximately 32% to 36% of patients in the FAME studies and 22 to 30% in the MEAD studies were pseudophakic at baseline. Additionally, the proportion of patients who had received prior treatment with VEGF inhibitors was low across all trials (FAME 4.2% to 7.5%, MEAD 4.3% to 10.4%). Hence, the efficacy and safety results presented may not adequately represent the population intended for PBS listing (pseudophakic lens or patients unsuitable for, contraindicated to, or have failed treatment with VEGF inhibitors).

### ***Comparative effectiveness***

- 6.11 The proportion of patients achieving  $\geq 15$  letter or  $\geq 10$  letter change from baseline in BCVA at 36 months in the key trials is presented in Table 4.

Table 4: Results: Proportion achieving  $\geq 15$  letter change and  $\geq 10$  letter change from baseline in BCVA at 36 months for FAME (full analysis population) and MEAD (intention to treat population).

Trial	0.2 $\mu$ g FA n/N (%)	DEX 700 $\mu$ g n/N (%)	Sham n/N (%)	Risk difference <sup>a</sup> (95% CI)	P-value
<b>Proportion achieving <math>\geq 15</math> letter change from baseline in BCVA at 36 months</b>					
<b>FA</b>					
FAME-001a	54/190 (28.4)	-	18/95 (18.9)	9.5 (-0.7, 19.6)	0.106
FAME-001b	54/186 (29.0)	-	17/90 (18.9)	10.1 (-0.2, 20.5)	0.086
Pooled	108/376 (28.7)	-	35/185 (18.9)	<b>9.8 (2.5, 17.1)</b>	<b>0.018</b>
<b>DEX</b>					
MEAD-010	-	36/163 (22.1)	22/165 (13.3)	<b>8.8 (0.5, 17.0)</b>	<b>0.038</b>
MEAD-011	-	42/188 (22.3)	20/185 (10.8)	<b>11.5 (4.1, 19.0)</b>	<b>0.003</b>
Pooled	-	78/351 (22.2)	42/350 (12.0)	<b>10.2 (4.7, 15.7)</b>	<b>&lt;0.001</b>
<b>Proportion achieving <math>\geq 10</math> letter change from baseline in BCVA at 36 months</b>					
<b>FA</b>					
FAME-001a	80/190 (42.1)	-	32/95 (33.7)	8.4 (-3.4, 20.2)	0.215
FAME-001b	82/186 (44.1)	-	30/90 (33.3)	10.8 (-1.3, 22.8)	0.105
Pooled	162/376 (43.1)	-	62/185 (33.5)	<b>9.6 (1.1, 18.0)</b>	
<b>DEX</b>					
MEAD-010	-	63/163 (38.7)	38/165 (23.0)	<b>15.6 (5.8, 25.4)</b>	<b>0.002</b>
MEAD-011	-	65/188 (34.6)	46/185 (24.9)	<b>9.7 (0.5, 0.18.9)</b>	<b>0.040</b>
Pooled	-	128/351 (36.5)	84/350 (24.0)	<b>12.5 (5.7, 19.2)</b>	<b>&lt;0.001</b>

Source: Table 22, p59; Table 23, p60; Table 30, p70; Table 31, p71 of the submission. *Calculated during evaluation.*

BCVA = best corrected visual acuity; CI = confidence interval; FA = fluocinolone acetonide; DEX = dexamethasone; n = number of participants with event; N = total participants in group; **Bold** = statistically significant.

<sup>a</sup> the submission reports negative risk difference; the commentary presents positive risk difference

- 6.12 The results of the pooled direct comparisons demonstrated that both FA and DEX were superior to sham treatment with regard to the proportion achieving  $\geq 15$  letter or  $\geq 10$  letter change from baseline in BCVA at 36 months.
- 6.13 The proportion of patients achieving  $\geq 15$  letter change from baseline in BCVA at 24 months (the primary endpoint in the FAME trial) in the FA treatment arm was 28.7% and in the sham treatment arm was 16.2% (RD 12.5% (95%CI: 5.5, 19.5)).
- 6.14 The mean change from baseline in BCVA Letter Score was calculated using two approaches: 1) the difference at baseline versus follow up and 2) as the change during the entire period of the study using an area under the curve (AUC) analysis. The results from the key trials are presented in Table 5.

Table 5: Mean change from baseline (36 months) in BCVA letter score in the study eye by treatment group (Integrated FAME Studies: full analysis population) and MEAD (intention to treat population).

	Active treatment		Sham		Mean difference (95% CI)	P-value
	N	Mean change ± SD	N	Mean change ± SD		
<b>Mean change from baseline (36 months) in BCVA letter score in the study eye by treatment group</b>						
<b>FA</b>						
FAME-001a	190	4.9 ± 19.2	95	3.3 ± 14.5	2.9 (-1.8, 7.5)	0.225
FAME-001b	186	5.7 ± 18.2	90	0.7 ± 16.4	<b>6.4 (1.7, 11.2)</b>	<b>0.008</b>
Pooled	376	5.3 ± 18.7	185	2.0 ± 15.4	<b>4.6 (1.3, 7.9)</b>	<b>0.007</b>
<b>DEX</b>						
MEAD-010	nr	4.13 ± 13.9	nr	0.79 ± 11.9	<b>3.3 (0.5, 6.1)</b>	nr
MEAD-011	nr	0.02 ± 17.8	nr	0.85 ± 13.6	-0.8 (-4.2, 2.6)	nr
Pooled	nr	2.06 ± 16.1	nr	0.82 ± 12.7	1.2 (-0.9, 3.4)	nr
<b>Mean BCVA average change (AUC approach) from baseline in the FAME trials, ETDRS letters (SD)</b>						
<b>FA</b>						
FAME-001a	190	4.5	95	2.3	nr	<b>0.003</b>
FAME-001b	186	5.8	90	0.9	nr	<b>&lt;0.001</b>
Pooled	nr	5.2	nr	Nr	nr	nr
<b>Mean BCVA average change (AUC approach) from baseline in the MEAD trial programme, ETDRS letters (SD)</b>						
<b>DEX</b>						
MEAD-010	nr	4.1 ± 8.3	nr	1.9 ± 7.7	nr	<b>0.016</b>
MEAD-011	nr	2.9 ± 8.6	nr	2.0 ± 8.2	nr	0.366
Pooled	nr	3.5 ± 8.4	nr	2.0 ± 8.0	nr	<b>0.023</b>

Source: Table 24, p62; Table 25, p63; Table 26, p64; Table 27, p65 of the submission; Table 3, p22 of the European Medicines Agency Assessment Report dexamethasone July 2014. *Modified during evaluation*

BCVA = best corrected visual acuity; CI = confidence interval; FA = fluocinolone acetonide; DEX = dexamethasone; n = number of participants with event; nr = not reported; N = total participants in group; SD = standard deviation; **Bold** = statistically significant results. Results are adjusted by baseline characteristics for FAME and MEAD, both studies used ANOVA.

- 6.15 The results of the pooled direct comparisons demonstrated that both FA and DEX were superior to sham treatment in regard to the mean change from baseline to 36 months in BCVA letter score using both the direct or AUC approach.
- 6.16 A summary of results of the indirect comparisons presented in the submission are shown in Table 6. During evaluation a number of errors in the calculations of the indirect comparison for the proportion of patients achieving a ≥15- or ≥10- letter improvement in BCVA were identified and these were corrected. In addition, the indirect comparison of the mean change from baseline in BCVA letter score was incorrectly calculated in the Executive Summary (-3.36 (-7.34, 0.62)) and in the main body of the submission (5.84 (1.86, 9.82)). The correct value is presented in Table 6. The Sponsor continued to present incorrect values (5.84 (1.86, 9.82)) in the pre-PBAC response.

**Table 6: Summary of results of the indirect comparisons presented in the submission for dichotomous and continuous outcomes**

Trial	Treatment n with event/N (%)	Common reference n with event/N (%)	Treatment effect (95% CI)	
			Odds Ratio (95% CI)	Risk Difference (95% CI)
<b>Dichotomous outcomes</b>				
Proportion achieving $\geq$ 15-letter improvement in BCVA				
FA vs. Sham [FAME]	108/376 (28.7)	35/185 (18.9)	<b>1.73 (1.12, 2.66)</b>	9.8 (2.5, 17.1)
DEX vs. Sham [MEAD]	78/351 (22.2)	42/350 (12.0)	<b>2.10 (1.39, 3.15)</b>	10.2 (4.7, 15.7)
Indirect comparison			0.82 (0.45, 1.49)	-0.4 (-9.3, 8.5)
Proportion achieving $\geq$ 10-letter improvement in BCVA				
FA vs. Sham [FAME]	162/376 (43.1)	62/185 (33.5)	<b>1.50 (1.04, 2.17)</b>	9.6 (1.1; 18.0)
DEX vs. Sham [MEAD]	128/351 (36.5)	84/350 (24.0)	<b>1.82 (1.31, 2.52)</b>	12.5 (5.7, 19.2)
Indirect comparison			0.82 (0.50, 1.35)	-2.9 (-14.6, 78)
<b>Continuous outcomes</b>				
	Treatment Mean change $\pm$ SD	Common reference Mean change $\pm$ SD	Mean difference (95% CI)	
Change from Baseline in BCVA Letter Score				
FA vs. Sham [FAME]	5.3 $\pm$ 18.75	2.0 $\pm$ 15.48	4.6 (1.3, 7.9)	
DEX vs. Sham [MEAD]	2.06 $\pm$ 16.1	0.82 $\pm$ 12.7	1.24 (-0.98, 3.47)	
Indirect comparison			3.36 (-0.62, 7.34) <sup>a</sup>	

Source: Tables 64, pp132-133; Table 65, p134 of the submission. *Calculated during evaluation*

BCVA = best corrected visual acuity; CI = confidence interval; n = number of participants with event; N = total number of participants; NA not applicable.

**Bold** = statistically significant.

<sup>a</sup> This result was recalculated during the evaluation.

6.17 Overall, there was no statistically significant difference in the indirect comparison between FA and DEX in the proportion of patients achieving  $\geq$  15-letter and  $\geq$  10-letter improvement in BCVA or in the change from baseline in BCVA letter score.

### **Comparative harms**

6.18 A range of safety results were presented in the submission. The risk management plan states that the most frequently reported adverse drug reactions included cataract operation, cataract and increased IOP. These adverse events are shown in Table 7. The occurrence of cataracts and/or the rate of cataract operation seen in the clinical trials will not be applicable to the PBS population, as the requested restriction for FA and the DEX PBS restriction specifies that patients must have had a cataract removed or be scheduled for cataract surgery.

**Table 7: Common ( $\geq 1.0\%$ ) Treatment-Emergent Ocular Adverse Events in the Study Eye (Integrated FAME Studies: Safety Population and MEAD Studies Pooled, Safety Population)**

Adverse event	0.2 µg/day FA (N = 375) n (%)	Sham (N = 185) n (%)	Risk difference (95%CI)	700 µg DEX N = 347 n (%)	Sham N = 350 n (%)	Risk difference (95%CI)
IOP increased	132 (35.2)	21 (11.4)	24 (17, 31)	116 (33.4)	23 (6.6)	27 (21, 33)
Cataract	171 (45.6)	53 (28.6)	17 (9, 25)	141 (40.6)	44 (12.6)	28 (22, 34)
Cataract nuclear	8 (2.1)	5 (2.7)	-1 (-3, 2)	nr	nr	-
Cataract operation	188 (50.1)	33 (17.8)	32 (25, 40)	21 (6.1)	10 (2.9)	3 (0, 6)
Cataract subcapsular	28 (7.5)	8 (4.3)	3 (-1, 7)	45 (13.0)	16 (4.6)	8 (4, 13)
Cataract cortical	nr	nr	-	11 (3.2)	11 (3.1)	0 (-3, 3)
Visual acuity reduced	39 (10.4)	17 (9.2)	1 (-4, 6)	33 (9.5)	18 (5.1)	4 (1, 8)
Visual impairment	13 (3.5)	7 (3.8)	0 (-4, 3)	5 (1.4)	4 (1.1)	0 (-1, 2)
Deaths	22.5 (6.0)	14.8 (8.0)	-2 (-7, 3)	9 (2.6)	5 (1.4)	1 (-1, 3)

Source: Table 48, pp101-103; Table 49, pp103-105 of the submission. *Calculated during evaluation.*

DEX = dexamethasone; FA = fluocinolone acetonide; IOP = intraocular pressure; n = number of participants reporting data; N = total participants in group; nr = not reported.

6.19 There were differences in the safety profile between the two populations in the trials with the proportion of patients with increase in intraocular pressure, cataracts and cataract operations higher for FA compared to DEX. The ESC considered the high rate of cataract surgery in the FA treatment arm was not informative, as the PBS population must have had cataract removed or be scheduled for cataract surgery in the affected eye.

### **Clinical claim**

6.20 The evaluation considered the claim of non-inferior effectiveness of FA versus DEX was not adequately supported due to:

- the potential risk of bias in the FAME trials (paragraph 6.6);
- the lack of a specified non-inferiority margin to determine non-inferiority (rather than basing the claim on a lack of statistical significance, paragraph 6.9); and
- the potential transitivity issues across the FAME and MEAD trials (paragraph 6.8); and
- the uncertain comparative effectiveness and safety in the population proposed for PBS listing (patients unsuitable for, contraindicated to, or have failed treatment with VEGF inhibitors) (paragraph 6.10).

6.21 The PBAC agreed with the ESC that overall, notwithstanding the issues listed above, FA appears non-inferior to DEX in terms of effectiveness, based on a mean difference in BCVA of 3.36 (-0.62, 7.34) letters. The PBAC noted it had previously indicated that “a mean BCVA change of -5 letters in the lower bound non-inferiority limit was probably reasonable” (paragraph 6.9) and the lower confidence interval (-0.62) supported non-inferiority.

6.22 The submission described FA as non-inferior in terms of safety compared to DEX. The evaluation considered this claim may not be adequately supported because IOP, cataracts and cataract operations were more frequent adverse events in the FA population. The PBAC agreed with the ESC that the more frequent adverse events

described were not informative, as the requested PBS patient population must have had a cataract removed or be scheduled for cataract surgery in the affected eye.

- 6.23 The PBAC considered the benefit was modest in terms of effectiveness for both DEX and FA with the risk difference for the proportion of patients achieving a  $\geq 10$ -letter or  $\geq 15$ -letter improvement in BCVA over 36 months versus sham injection ranging from 9.6% to 12.5%. However, the PBAC considered the claim of non-inferior comparative effectiveness was reasonable.
- 6.24 The PBAC considered that the claim of non-inferior comparative safety was uncertain because the clinical data provided was not in the proposed PBS population (i.e. have had, or are scheduled for, cataract removal) but, on balance, was likely to be reasonable.

### **Economic analysis**

- 6.25 The submission presented a cost-minimisation analysis (CMA) using the published dispensed price for maximum quantity (DPMQ) for DEX. It is noted that pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. The CMA should have used the published AEMP for DEX to determine the price for FA.
- 6.26 Results of the CMA based on published prices are shown in Table 8.

**Table 8: Results of the cost minimisation analysis conducted by the submission (using DPMQ values)**

	Fluocinolone acetonide	Dexamethasone
Drug cost	\$9,486.83	\$8,781.57
Administration costs (ophthalmologist visit, steroid administration, optical coherence tomography, fluorescein angiography).	\$1,143.69	\$2,680.78
Other therapies (laser treatment, intravitreal steroids, VEGF inhibitors*).	\$938.93	\$200.52
IOP-lowering medication and surgical interventions	\$121.90	\$28.49
Total cost	\$11, 691.35	\$11, 691.35

Source: Table 56, pp155-156 of the submission.

\*Costs in the submission are based on a weighted average published DPMQ of aflibercept 4mg \$1,096.21, ranibizumab 1.65 mg \$1,042.60.

- 6.27 The submission proposed equi-effective doses of FA 190  $\mu\text{g}$  1 administration per 36 months and DEX 700  $\mu\text{g}$  6.48 administrations per 36 months. This dose relativity is inappropriate because it does not reflect the clinical trial data provided in the submission. The PBAC noted the equi-effective doses were 1.3 administrations for FA and 4.11 administrations of DEX over 36 months based on the clinical trial data presented in the submission that supported the claim of non-inferiority.
- 6.28 The submission claimed that patients would receive VEGF inhibitors rather than another FA implant if they require retreatment. The CMA assumed only one VEGF inhibitor injection would be received per patient (i.e. one month of treatment), which may not be reasonable and no data were provided to support this assumption.

- 6.29 The CMA assumed 11.04 ophthalmologist visits for patients treated with FA and 14.42 for patients treated with DEX over 36 months. The methodology for calculating the number of ophthalmologist visits was uncertain and the assumptions applied were not justified in the submission. The PBAC agreed with ESC that the number of ophthalmology visits over 36 months for patients receiving either FA or DEX should not be different.
- 6.30 The CMA included the cost of concomitant use of VEGF inhibitors and intravitreal steroids for FA and DEX. The submission applied the rates of concomitant treatment observed in the FAME studies (3.2% for VEGF inhibitors, 8.2% for intravitreal steroids) to FA and assumed a rate of treatment (2.7% for VEGF inhibitors, 6.9% for intravitreal steroids) for DEX. The ESC considered the estimated proportions of use were highly uncertain and the assumption only one injection of VEGF inhibitors or intravitreal steroids would be received per patient over the 36 month timeframe was poorly supported.
- 6.31 The CMA included the cost of IOP lowering medication for 38.4% of patients treated with FA and 41.5% of patients treated with DEX. Although this cost was minimal, these rates appear to be inconsistent with the rates of IOP increased presented in Table 7 (35.2% for FA and 33.4% for DEX), as a greater proportion of patients were taking IOP-lowering medication compared with the proportion identified with increased IOP. The ESC noted that this would be unlikely to have a significant impact on the CMA.
- 6.32 Given the non-inferiority claims have been accepted by the PBAC (paragraphs 6.23 and 6.24), the cost per patient for treatment with FA should be no more than the cost per patient of DEX. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

**Drug cost/patient/treatment: \$9,487**

- 6.33 The cost per patient over 36 months (based on the published DPMQ) for FA and DEX is presented in Table 9.

**Table 9: Drug cost per patient for proposed and comparator drugs (published DPMQ)**

	FA		DEX	
	Trial dose and duration	CMA and financial estimates	Trial dose and duration	CMA and financial estimates
Dose per implant	190 µg		700 µg	
Average number of implants (36 months)	1.3 <sup>a</sup>	1	4.11 <sup>b</sup>	6.48
Drug cost/patient	\$12,333	\$9,487	\$5,570	\$8,782
Cost/ patient including administration cost*	\$12,671	\$9,747	\$6,638	\$10,465

Source: Table 39, p81 of the submission, Table 40 p82 of the submission. *Italics calculated during evaluation.*

CMA = cost minimisation analysis; DEX = dexamethasone; DPMQ = dispensed price for maximum quantity; FA= fluocinolone acetonide

<sup>a</sup> total treatments/n=489/376 = 1.30 FA CSR

<sup>b</sup> total treatments/n=1427/347 = 4.11 DEX

\* \$259.75 per administration

### **Estimated PBS usage & financial implications**

6.34 This submission was not considered by DUSC.

6.35 The submission used an epidemiological approach. No justification for this approach was provided in the submission and the evaluation considered a market-share approach may have been more appropriate. The PSCR stated that an epidemiological approach was used on the basis that DEX was underutilised and there is non-PBS usage of intravitreal triamcinolone acetonide. The ESC considered that this was not unreasonable but the extent of any underutilisation was highly uncertain. The Sponsor argued for projected market growth due to switching from triamcinolone acetonide to FA with an increase in adherence due to FA listing. The ESC considered the assumption of substantial market growth may not be reasonable given there is a low clinical need and FA is a second line therapy with inferior effectiveness and safety compared to VEGF inhibitors. The key input parameters for financial estimates are shown in Table 10.

**Table 10: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Estimation of the number of patients with diabetes	Prevalence of diabetes 4.9%: National Health Survey: 2017-18. Applied to Australian population, all ages (ABS data).	Likely overestimated because it was applied to the total population rather than the adult population.
Estimation of the number of patients with DMO	2.77% prevalence, 0.25% incidence: Minassian <i>et al.</i> 2012	Likely overestimated due to double counting with the incident population added to the prevalent population.
Uptake rate	20% in Year 1 increasing to 70% in Year 6. Assumption that majority will switch to FA and rate will increase over time.	Likely overestimated rapid uptake of the implant.
Retreatment at 36 months	Two rates applied: 8.94% based on the number in the extension divided by the sum of the two FAME patient numbers and 18.03% based on the number in the extension study divided by the number in FAME-001a	Likely overestimated due to double counting*.
Number of scripts per person	1.3 scripts of FA per person to account for 30% of patients receiving an implant in both eyes	Assumption not justified in the submission.

Source: Table 78, p162; Table 79, p163 of the submission. File named: luvien\_utilisation-and-cost-minimisation\_Nov2019.

\* There appears to be some double counting of scripts by calculating retreated patients in the sheet "2. Patients" and again in "3a. Scripts new".

6.36 The net financial implications of listing FA on the PBS/RPBS (based on the published price of DEX) is shown in Table 11.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts*	█	█	█	█	█	█
<b>Estimated financial implications of FA</b>						
Cost to PBS/RPBS less co-payments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost of displaced drugs to PBS/RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS/ Services Australia/other	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS/MBS/Services Australia	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: File named: lluvien\_utilisation-and-cost-minimisation\_Nov2019.

\* The model assumed each patient received 1.3 scripts to account for 30% of patients receiving an implant in each eye. There appears to be some double counting of scripts by calculating retreated patients in the sheet "2. Patients" and again in "3a. Scripts new".

6.37 The net cost to the PBS/RPBS of listing FA was estimated to be less than \$10 million in Year 1, and a total of \$30 – \$60 million in the first 6 years of listing, based on published prices. The PBAC agreed with the ESC that the net cost to the PBS/RPBS was high in the context of cost-minimisation. The PBAC noted a contributing factor to the high net cost was the calculation of the budget impact using a FA price derived from an inappropriate equi-effective dose as described in paragraph 6.27.

6.38 The total net cost to the health budget was uncertain due to the following:

- Retreatment was assumed at year three for a proportion of patients (8% to 18%) whereas the trial demonstrated that a proportion (26%) of patients were receiving retreatment prior to year three;
- The use of both prevalent and incident DMO population leads to double counting of the number of eligible patients;
- The use of the prevalent DMO population leads to patients being treated three times in three years rather than once over a three-year period;
- The proportion of patients who have had (or were scheduled for) cataract surgery as defined by the proposed PBS listing was not accounted for;
- The number of ophthalmologist visits for FA and DEX (11.04 and 14.42, respectively), may not be reasonable and is likely to be very similar.

### Quality Use of Medicines

6.39 The submission provided a copy of European Risk Management Plan (RMP) for FA and the Australian Specific Annex. The key aspect of the proposed risk management plan was the IRISS study which was a European, multicentre, open-label, observational registry study of patients treated with the FA implant for any reason. The study was registered at ClinicalTrials.gov (NCT01998412). The observation phase is ongoing, with a planned duration of follow-up of 5 years. The submission stated that FA has been available in international markets for several years and multiple post marketing

studies are available that support the use in clinical practice. No further Australian post-marketing surveillance studies are planned.

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

- 6.40 No risk-sharing arrangement (RSA) was proposed in the submission. The PBAC noted an RSA with subsidisation caps was recommended for DEX with a rebate in place to account for use beyond the utilisation estimates presented in the submission (paragraph 7.9, DEX PSD, March 2016 PBAC meeting).

*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 FA for the treatment of DMO in patients who are unsuitable for, contraindicated to, or have failed treatment with VEGF inhibitors. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of FA would be acceptable if it were cost-minimised against DEX.
- 7.2 The PBAC noted the equi-effective doses proposed in the submission were not based on the clinical evidence presented to support the non-inferiority claim and considered this was not appropriate. The PBAC advised the equi-effective doses should be 1.3 administrations of FA and 4.11 administrations of DEX over 36 months as this reflects the mean doses in the MEAD and FAME studies presented in the submission.
- 7.3 The PBAC advised the proposed restriction in Section 3.1 was appropriate with the following amendments:
- Given the lack of benefit, retreatment with FA should not be allowed within 36 months and this should be specified in the restriction criteria (paragraph 3.4).
  - Addition of the clinical criteria "Patient must have been treated with a course of topical or intra-ocular corticosteroids and did not experience a clinically significant rise in intraocular pressure" to reflect the wording in the approved Product Information (paragraph 3.2).
  - The PBAC noted the proposed listing lowered the limit of BCVA letter score for treatment initiation from 39 to 20, thereby broadening the eligibility criteria for treatment compared to DEX and the VEGF inhibitors. The PBAC noted that, while the FAME trials included patients with a BCVA letter score of >20, it was not clear in the submission how many patients had a score of 20 to 39 at baseline. The PBAC considered allowing a lower BCVA limit of 20 may address an unmet clinical need and may be appropriate. However the PBAC considered there was insufficient information provided regarding the efficacy and cost-effectiveness of treating patients with a baseline score of 20 to 39 letters and the financial implications of changing the restriction were unknown. The PBAC considered the initial restriction criteria for FA should be consistent with the criteria for DEX and require a BCVA letter score of between 78 and 39.

- 7.4 The PBAC noted the claim that FA was of non-inferior effectiveness and safety versus DEX was supported by an indirect comparison of two pooled randomised studies for each product using sham injection as a common treatment arm. The change from baseline in BCVA letter score was 3.36 (95% CI -0.62, 7.34) in favour of FA, with the lower CI falling inside a non-inferiority margin of -5 letters previously accepted by the PBAC. The PBAC considered that while there were transitivity (paragraph 6.8) and applicability (paragraph 6.10) issues with the indirect comparison, on balance, the claim of non-inferior effectiveness was supported.
- 7.5 The PBAC noted there were differences in the safety profile between the two populations in the trials, with the proportion of patients with increase in IOP, cataracts and cataract operations higher for FA compared to DEX. However, the PBAC considered the high rate of cataract surgery in the FA treatment arm was not informative, as the PBS population must have had a cataract removed in the treated eye or be scheduled for cataract surgery in the treated eye. The PBAC acknowledged FA and DEX were likely to have a similar safety profile in the proposed PBS population and accepted the claim of non-inferior safety.
- 7.6 The PBAC noted the modest benefit of FA and DEX (paragraph 6.23) and recalled that DEX was recommended on the basis of having inferior effectiveness and safety compared to the VEGF inhibitors. The PBAC reiterated that DEX and FA should not be considered as alternative therapies to the VEGF inhibitors.
- 7.7 The PBAC recommended that the revised equi-effective doses (paragraph 7.2) should be applied in the CMA using the effective price of DEX. The PBAC considered the CMA should only include the cost of drug and the cost of administering the implants. The PBAC considered all other costs were highly uncertain, not well justified in the submission (paragraph 6.28 to 6.31) and should not be included in the CMA.
- 7.8 The PBAC considered the financial estimates provided in the submission were unreliable (paragraphs 6.35, 6.37 and 6.38). The PBAC considered that a market share approach would have been more appropriate to estimate the use of this medicine. The PBAC considered there was a low clinical need and listing FA on the PBS was unlikely to substantially grow the market. The PBAC considered that listing FA for DMO on a cost minimisation basis with DEX using effective prices and the equi-effective doses recommended (paragraph 7.2) would be cost-neutral to the PBS. The PBAC considered that inclusion of FA in the DEX RSA (paragraph 7.9) would manage any residual uncertainty regarding the financial estimates.
- 7.9 The PBAC noted DEX has a SPA and a RSA with a rebate in place to account for use beyond the utilisation estimates presented in the DEX submission (paragraph 7.9, DEX PSD, March 2016 PBAC meeting). The PBAC advised that FA would be required to join the DEX RSA with no changes to the expenditure caps.
- 7.10 The PBAC recommended that FA should not be treated as interchangeable with any other drugs.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and

advised that, because FA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

- 7.12 The PBAC advised that FA not suitable for prescribing by nurse practitioners.
- 7.13 The PBAC considered that the Early Supply Rule should not apply to FA.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max.Qty (Units)	Max. Qty (Packs)	No.of Rpts	PBS item code	Proprietary Name and Manufacturer	
Fluocinolone acetonide 190 microgram implant, 1	1	1	0	NEW	Iluvien®	Specialised Therapeutics Alim Pty Ltd

<b>Category / Program:</b> 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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing Only
<b>Indication:</b> Diabetic macular oedema (DMO)
<b>Treatment Phase:</b> Initial treatment
<b>Treatment criteria:</b> <ul style="list-style-type: none"> <li>▪ Must be treated by an ophthalmologist or in consultation with an ophthalmologist</li> </ul>
<b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ Patient must have visual impairment due to diabetic macular oedema <b>AND</b></li> <li>▪ Patient must have been treated with a course of topical or intra-ocular corticosteroids and did not experience a clinically significant rise in intraocular pressure <b>AND</b></li> <li>▪ Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment <b>AND</b></li> <li>▪ The condition must be diagnosed by optical coherence tomography; or</li> <li>▪ The condition must be diagnosed by fluorescein angiography <b>AND</b></li> <li>▪ Patient must have a contraindication to vascular endothelial growth factor (VEGF) inhibitors; or</li> <li>▪ Patient must be unsuitable for treatment with VEGF inhibitors; or</li> <li>▪ Patient must have failed prior treatment with VEGF inhibitors</li> </ul>
<b>Population criteria:</b> <ul style="list-style-type: none"> <li>▪ Patient must have had a cataract removed in the treated eye; or</li> </ul>

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<ul style="list-style-type: none"> <li>▪ Patient must be scheduled for cataract surgery in the treated eye</li> </ul>
<p><b>Prescribing Instructions:</b>            Authority approval for initial treatment of each eye must be sought.            The first authority application for each eye must be made in writing or by telephone.            A written application must include:            a) a completed authority prescription form;            b) a completed Diabetic Macular Oedema (DMO) - PBS Supporting Information Form; and            c) a copy of the optical coherence tomography or fluorescein angiogram report.</p> <p>A telephone application must be made following submission by facsimile of a copy of a completed Diabetic Macular Oedema (DMO) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.</p> <p>Authority applications for the same eye will be limited to 1 application per 36 month period.</p>
<p><b>Administrative Advice:</b>            Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:            Department of Human Services            Complex Drugs            Reply Paid 9826            HOBART TAS 7001</p> <p>The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.</p> <p>Special Pricing Arrangements apply.</p>

<p><b>Category / Program:</b> General Schedule (Code GE)</p>
<p><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</p>
<p><b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency</p>
<p><b>Indication:</b> Diabetic macular oedema (DMO)  <b>Treatment Phase:</b> Continuing treatment  <b>Treatment criteria:</b></p> <ul style="list-style-type: none"> <li>▪ Must be treated by an ophthalmologist or in consultation with an ophthalmologist</li> </ul> <p><b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>▪ Patient must have previously been issued with an authority prescription for this drug for the same eye</li> </ul>
<p><b>Prescribing Instructions:</b>            Authority applications for the same eye will be limited to 1 application per 36 month period.</p>
<p><b>Administrative Advice:</b>            Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Special Pricing Arrangements apply.</p>

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **9 Context for Decision**

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

## **10 Sponsor's Comment**

The sponsor had no comment.