7.11 FLUOCINOLONE ACETONIDE, Intravitreal injection 190 micrograms, Iluvien®, Specialised Therapeutics Alim Pty Ltd.

1 Purpose of Application

1.1 At the March 2020 meeting, the PBAC recommended an Authority Required listing for fluocinolone acetonide (FA) for the treatment of diabetic macular oedema (DMO) who are unsuitable for, contraindicated to, or have failed treatment with vascular endothelial growth factor (VEGF) inhibitors. The recommendation was on the basis of a cost-minimisation analysis (CMA) versus dexamethasone (DEX) intravitreal implant, using clinical evidence from an indirect comparison.

1.2 The minor resubmission requested an amendment to the PBAC's previously recommended equi-effective doses of 1.3 administrations of FA versus 4.1 administrations of DEX over 36 months (paragraph 7.2, FA Public Summary Document [PSD], March 2020). Unchanged from the March 2020 submission, the Sponsor proposed in the resubmission that the equi-effective dose should be 1 administration of FA versus 6.48 administrations of DEX over 36 months.

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).

Previous PBAC consideration

2.2 At its March 2020 meeting, 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 (paragraph 7.1, FA PSD, March 2020).

2.3 The PBAC recommended the equi-effective doses should be 1.3 administrations of FA and 4.11 administrations of DEX over 36 months based on the mean doses in the MEAD and FAME studies, given the clinical claim of non-inferiority between FA and DEX was based on an indirect comparison using the same trials (paragraph 7.2, FA PSD, March 2020).

2.4 Table 1 provides a summary of the key issues identified by the PBAC at the March 2020 meeting and the manner in which the minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in March 2020 and how they were addressed in the minor resubmission

Matters of concern from March 2020	How the November 2020 resubmission addresses it
[paragraph 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.	The Sponsor has stated that patients treated with FA would receive 1 implant over 36 months, which is consistent with most patients with breakthrough oedema being treated with an anti-VEGF therapy and not an additional FA implant. The Sponsor has stated that patients treated with DEX would receive 6.48 implants over 36-months, which is consistent with the PBAC's previous recommendation regarding Ozurdex (paragraph 6.34, DEX PSD, March 2016), the clinical data presented in Section 2 and Australian clinical practice. The Sponsor has reiterated the claim from the March 2020 submission that the appropriate equi-effective dose is 1 dose FA and 6.48 doses DEX over 36 months.
[paragraph 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.	The Sponsor has specified in the CMA that FA patients will have 1 ophthalmologist visit and DEX patients will have 6.48 ophthalmologist visits over 36 months.
[paragraph 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.	The Sponsor has specified in the CMA that FA patients will have 1 administration of intravitreal steroids and DEX patients will have 6.48 administrations of intravitreal steroids. The Sponsor has specified in the CMA that the same proportion of patients retreated with FA in the FAME studies will instead be treated with concomitant anti-VEGF therapy for breakthrough oedema within 36 months, and DEX patients will not be treated with concomitant anti-VEGF therapy during the treatment period.

CMA = cost minimisation analysis; DEX = dexamethasone; FA = fluocinolone acetate; PSD = Public Summary Document; VEGF = vascular endothelial growth factor.

Source: Compiled during the evaluation. Paragraph references for March 2020 refer to the fluocinolone Public Summary Document.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested the following listing in the resubmission. The Sponsor agreed to the restriction recommended by the PBAC at its March 2020 meeting.

Name, Restriction, Manner of administration and form	Max.Qty (Units)	Max. Qty (Packs)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Fluocinolone acetonide 190 microgram implant, 1	1	1	0	$[redacted] (effective); $9,449.08 (published)	Iluvien®	Specialised Therapeutics Alim Pty Ltd

Category / Program: General Schedule (Code GE)

Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Restriction Level / Method: ☒ Authority Required – In Writing Only

Indication: Diabetic macular oedema (DMO)

Treatment Phase: Initial treatment

Treatment criteria:

- Must be treated by an ophthalmologist or in consultation with an ophthalmologist

Clinical criteria:

- Patient must have visual impairment due to diabetic macular oedema

  AND
- 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

  AND
- 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

  AND
- The condition must be diagnosed by optical coherence tomography; or
- The condition must be diagnosed by fluorescein angiography

  AND
- 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

Population criteria:

- Patient must have had a cataract removed in the treated eye; or
- Patient must be scheduled for cataract surgery in the treated eye

Prescribing Instructions:

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.

Authority applications for the same eye will be limited to 1 application per 36 month period.

Administrative Advice: 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 www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 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. Special Pricing Arrangements apply.

Category / Program: General Schedule (Code GE)
Prescriber type: ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Restriction Level / Method: ☒ Authority Required – Telephone/Electronic/Emergency
Indication: Diabetic macular oedema (DMO) **Treatment Phase:** Continuing treatment **Treatment criteria:** ▪ Must be treated by an ophthalmologist or in consultation with an ophthalmologist **Clinical criteria:** ▪ Patient must have previously been issued with an authority prescription for this drug for the same eye
Prescribing Instructions: Authority applications for the same eye will be limited to 1 application per 36 month period.
Administrative Advice: 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). Special Pricing Arrangements apply.

4 Comparator

4.1 The March 2020 submission nominated DEX as the comparator (paragraph 5.1, FA PSD, March 2020), 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 minor resubmission did not update the proposed comparator.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from 3 health care professionals (HCPs) via

the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with FA, including access for suitable patients who are recalcitrant to other forms of treatment. The HCPs commented that FA reduces burden of treatment and frequency of intravitreal injections, as well as the risk of infection, and that it has associated productivity and efficiency gains. They stated that a longer lasting injection would be of benefit to patients, especially those who currently have to come every month for an injection, and that they have been waiting for it to be available in Australia after seeing its success in the United States.

Clinical trials

5.3 The March 2020 submission was based on an indirect comparison of four randomised trials (RCTs): a pooled analysis of two identical trials comparing FA to sham injection (FAME-001a; N=190 and FAME-001b; N=186) and a pooled analysis of two identical trials comparing DEX to sham injection (MEAD-010; N=163 and MEAD-011; N=188), in patients with DMO. No new clinical evidence was presented in the minor resubmission. Details of the trials presented in the March 2020 submission can be found in Table 2, FA PSD, March 2020.

Clinical claim

5.4 The March 2020 submission described FA as non-inferior in terms of effectiveness and safety compared with DEX. The minor resubmission did not update the clinical claim.

5.5 The PBAC previously considered that FA was non-inferior in terms of comparative efficacy to DEX, based on the indirect comparison of two pooled randomised studies for each product using sham injection as a common treatment arm (paragraph 7.4, FA PSD, March 2020). The PBAC considered that while there were transitivity and applicability issues with the indirect comparison, on balance, the claim of non-inferior effectiveness was supported.

5.6 The PBAC previously considered that FA was non-inferior in terms of comparative safety to DEX (paragraph 7.5, FA PSD, March 2020). While there were differences in the safety profile between the two populations in the trials, 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.

Equi-effective doses

5.7 The March 2020 submission claimed that 1 dose of FA would replace 6.48 doses of DEX over 36 months, while maintaining the same efficacy. 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 (paragraph 7.2, FA PSD, March 2020).

5.8 The Sponsor presented the following rationale in the minor resubmission for requesting the PBAC to reconsider the equi-effective doses of FA and DEX:

- Retreatment with FA in the FAME studies does not reflect clinical practice:

  - FA patients who experience breakthrough oedema would be treated with anti-VEGF therapy in clinical practice, not another FA implant. The proposed restriction for FA prohibits retreatment within 36 months. The Secretariat noted that the approved Product Information (PI) for FA states in the Dose and Method of Administration section, "An additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema." The dosing of FA described in the PI is consistent with the FAME trials (1.3 doses over 36 months). The PI is also consistent with less frequent dosing in accordance with the equi-effective dose requested by the Sponsor (1 dose over 36 months), but the Sponsor's request is not supported by relevant clinical trial results.

- Retreatment with DEX in the MEAD studies does not reflect clinical practice:
  - Australian retinal experts state that the duration of effect for DEX is 3 to 4 months, as reflected in the BEVORDEX trial. The Secretariat noted that the BEVORDEX trial was designed for patients to receive bevacizumab every 4 weeks vs DEX every 4 months (i.e. the BEVORDEX trial design stipulated more frequent DEX dosing compared to the MEAD trials). The Sponsor has not presented any additional RCTs to support increased DEX dosing in the context of an indirect comparison against FA using sham injection as a common reference.
  - PBS use of DEX post listing is higher than the number of treatments in the MEAD trial, where retreatment within 6 months was not allowed and patients requiring additional therapies were withdrawn. The Secretariat noted that the approved PI for DEX states in the Dose and Method of Administration section, "In clinical trials, the majority of retreatments were administered between 5 and 7 months after a prior treatment. Patients in the OZURDEX® arm of the pivotal trials received an average of 4 implants over 3 years. The protocol in the pivotal trials specified a 6-monthly dosing interval." The PI is consistent with the MEAD trials (4.11 doses over 36 months), and inconsistent with the Sponsor's request for more frequent dosing (6.48 doses over 36 months).
- The results of the indirect comparison between FA and DEX suggest that FA had a greater and consistent improvement with respect to mean change in best-corrected visual acuity (BCVA). Also, intermittent dosing with DEX, as used in the MEAD study, results in clinical fluctuations and anatomical fluctuations (centre point thickness) that are not seen with FA. The Secretariat noted the PBAC accepted in March 2020 that FA is non-inferior to DEX, consistent with the Sponsor's clinical claim. While the PBAC considered the benefit was modest in terms of effectiveness for both DEX and FA, it

considered the claim of non-inferior comparative effectiveness was reasonable (paragraph 6.23, FA PSD, March 2020).

- Patients with DMO have a high risk of non-adherence, which is eliminated by the longer acting FA implant.
- Aboriginal and Torres Strait Islander peoples will experience a reduced burden with FA with respect to accessing clinical services, especially in remote areas.

5.9 The Sponsor presented the following sources of evidence and retrospective clinical data in the minor resubmission to support the claim that DEX is used more frequently than every 6 months in clinical practice:

- Patients treated with DEX would receive 6.48 implants over 36-months, which is consistent with the PBAC's previous recommendation regarding DEX (paragraph 6.34, DEX PSD, March 2016). The Secretariat noted that this recommendation was associated with clinical trial evidence from DEX, ranibizumab, aflibercept, sham injection, bevacizumab and laser photocoagulation. The equi-effective dose was ultimately derived from DEX and ranibizumab/aflibercept, with the price of DEX determined to be lower than the cost of the cheapest PBS-listed VEGF inhibitor treatment over 36 months. This comparison is not applicable to an equi-effective dose derived from RCT evidence of DEX versus FA using sham injection as a common reference.
- Drug Utilisation Sub-Committee (DUSC) review of ranibizumab and aflibercept (May 2018). This review calculated the average number of DEX injections for DMO per prevalent patient in 2017 was 2.21 over 12 months.
- Prescription data using a 10% PBS sample (update of DUSC review by HI Connections). This analysis found 2.4 DEX injections per prevalent patient over 12 months.
- Audit of Australian Pharmacy Database (iCare Pharmacy) of all eyes treated with DEX for DMO only. This source reported the mean DEX use was 2.3 injections over 12 months. For continuing therapy only, the mean DEX use was 2.6 injections over 12 months.
- AUSSIEDEX Phase IV study of DEX implants in Australia. This study reported 2.3 injections of DEX over 12 months.

5.10 The PBAC Guidelines (version 5.0, 2016) state in Section 3B.2 'Estimation of equi-effective doses'[1] that the following sources of evidence should be used (presented in order of preference):

[1] https://pbac.pbs.gov.au/section-3b/3b-2-estimation-of-equi-effective-doses.html

- Direct randomised trials where doses of both medicines are titrated against a response, or where doses of both medicines are fixed if the medicines are given in regular clinical practice according to a fixed protocol used in the trials;
- Direct randomised trials where doses of one or both medicines are arbitrarily fixed in a way that does not reflect regular clinical practice. …;
- Indirect comparisons of two or more sets of randomised trials involving one or more common references;
- Nonrandomised studies where both dose and effect are measured;
- Nonrandomised studies (including market research data) where dose, but not effect, is measured. This source of evidence is the least preferred. It may be preferable to calculate doses from prescribing or dispensing data, such as the PBS prescription dataset, rather than using market research data.

5.11 The Sponsor acknowledged in their pre-PBAC response the PBAC's preference for an indirect comparison using randomised trials (FAME and MEAD) over evidence from nonrandomised studies for the calculation of equi-effective doses; however, the Sponsor reiterated that the trial doses are not representative of Australian and global clinical practice. The Sponsor also restated in the pre-PBAC response that the results of the indirect comparison suggest that patients treated with the FA implant had a greater improvement in BCVA compared with the DEX implant.

Economic analysis

5.12 The March 2020 submission presented a CMA of FA to DEX based on an indirect comparison using the randomised trials FAME and MEAD. The equi-effective doses were estimated by the Sponsor as FA 190 μg 1 administration per 36 months and DEX 700 μg 6.48 administrations over 36 months. The PBAC considered this dose relativity to be inappropriate because it did 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 that supported the claim of non-inferiority (paragraph 6.27, FA PSD, March 2020).

5.13 The March 2020 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 the PBAC considered may not be reasonable (paragraph 6.28, FA PSD, March 2020).

5.14 The March 2020 submission assumed 11.04 ophthalmologist visits for patients treated with FA and 14.42 for patients treated with DEX over 36 months. 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 (paragraph 6.29, FA PSD, March 2020).

5.15 The PBAC advised in March 2020 that 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 and should not be included in the CMA (paragraph 7.7, FA PSD, March 2020).

5.16 The minor resubmission presented a CMA that the Sponsor states is consistent with the approach used in the March 2020 submission, using only drug costs and the costs associated with administration. Results of the CMA based on effective[2] prices are shown in Table 2.

Table 2: Results of the cost minimisation analysis conducted by the minor resubmission

		DEX	FA	Source/calculation
A	Ex-manufacturer price (effective)	$[redacted]	$[redacted]	DEX = ex-manufacturer price FA = C / B
B	Injections	6.48	1	DEX = DEX PSD, March 2016 FA = Assumption[a]
C	Drug costs	$[redacted]	$[redacted]	DEX = A * B FA = E – (D + E + F)
	Administration costs:[b]			
D	Ophthalmologist visits	$247.86	$38.25	FA and DEX = B * $38.25 (MBS Item 105)
E	Steroid administration	$1,708.45	$263.65	FA and DEX = B * $263.65 (MBS Item 42740)
	Other therapies:			
F	Anti-VEGF	-	$381.27	Not stated
G	Total cost	$[redacted]	$[redacted]	DEX = C + D + E + F FA = assumed equal to DEX

Source: Table 10, p26 of the minor resubmission.
DEX = dexamethasone; FA = fluocinolone acetonide; MBS = Medical Benefits Schedule; PSD = Public Summary Document; VEGF = vascular endothelial growth factor.
[a] Assumes that FA patients who experience breakthrough oedema would be treated with anti-VEGF therapy, not another FA implant.
[b] The Sponsor has used 85% cost of MBS Items 105 and 42740. The economic evaluation should use 100% of the MBS schedule fee. This is consistent with the PBAC Guidelines (Table 3A.6.1, p84) and the Manual of Resource Items and Associated Unit Costs (December 2016) which states "The unit costs to be used for medical services in an economic evaluation are the Schedule Fees as presented in the MBS") (Section 5, p12).

5.17 The CMA in the minor resubmission maintained that the equi-effective doses are 1 FA implant versus 6.48 DEX implants over 36 months.

5.18 The CMA in the minor resubmission assumed that patients treated with the FA implant who experience breakthrough oedema would be treated with anti-VEGF agents. According to the proposed restriction criteria for FA, patients treated with FA must have a contraindication to or be unsuitable for anti-VEGF therapy, or have failed prior treatment with VEGF inhibitors.

5.19 The CMA in the minor resubmission assumed 1 ophthalmologist visit for patients treated with FA and 6.48 for patients treated with DEX over 36 months. The methodology for calculating the number of ophthalmologist visits corresponds to the relative equi-effective doses proposed by the Sponsor.

[2] Since FA received a positive recommendation at the March 2020 PBAC meeting, the effective price of DEX is known by the Sponsor.

5.20 The CMA in the minor resubmission assumed 1 steroid administration for patients treated with FA and 6.48 for patients treated with DEX over 36 months. The methodology for calculating the number of steroid administrations corresponds to the relative equi-effective doses proposed by the Sponsor.

5.21 In consideration of the minor resubmission, the PBAC reaffirmed its view from March 2020 that the cost minimised price of FA should be cost neutral to Government, based on the following criteria:

- The equi-effective doses should be 1.3 administrations for FA and 4.11 administrations of DEX over 36 months (paragraph 5.12);
- Anti-VEGF injections for breakthrough oedema in FA patients should not be included in the CMA (paragraphs 5.13 and 5.15);
- Ophthalmologist visits for FA and DEX patients should not be different and therefore do not need to be included in the CMA (paragraph 5.14);
- Inclusion of the cost of administering the implants in the CMA was reasonable (paragraph 5.15), and the relative number of FA and DEX administrations should correspond with the equi-effective doses (1.3 FA:4.11 DEX).

Drug cost/patient/administration: $[redacted]

5.22 The cost per patient over 36 months (based on the effective DPMQ) for FA and DEX is presented in Table 3.

Table 3: Drug cost per patient for proposed and comparator drugs (effective 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[a]	1	4.11[b]	6.48
Drug cost/patient[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost/patient including administration cost[d]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 39, p81 of the submission, Table 40 p82 of the submission.
CMA = cost minimisation analysis; DEX = dexamethasone; DPMQ = dispensed price for maximum quantity; FA = fluocinolone acetonide.
[a] total treatments/n=489/376 = 1.30 FA.
[b] total treatments/n=1427/347 = 4.11 DEX.
[c] Effective DPMQ for FA is $[redacted] and for DEX is $[redacted]
[d] $263.65 per administration (85% MBS Item 42740).

5.23 The PBAC considered in March 2020 that given the non-inferiority claims have been accepted by the PBAC, the cost per patient for treatment with FA should be no more than the cost per patient of DEX (paragraph 6.32, FA PSD, March 2020). 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. The PBAC reiterated this principle with reference to the minor resubmission.

Estimated PBS usage & financial implications

5.24 The March 2020 submission used an epidemiological approach to estimate the financial implications of listing FA; however, the PBAC considered the financial estimates provided in the submission were unreliable (paragraph 7.8, FA PSD, March 2020). 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 would be cost-neutral to the PBS.

5.25 The minor resubmission retained an epidemiological approach for the estimation of PBS usage and financial implications. The resubmission stated the following issues were addressed from the March 2020 meeting:

- The PBAC considered that the prevalence of diabetes (4.9%) was likely overestimated because it was applied to the total population rather than the adult population. The resubmission addressed this issue by applying the prevalence to the adult population only.
- The PBAC considered that the number of patients with DMO was likely overestimated due to double counting, with the incident population (0.25%) added to the prevalent population (2.77%). The resubmission addressed this issue by only including the prevalent population for the first year of listing and only including incident patients for subsequent years.
- The PBAC considered that retreatment at 36 months was likely overestimated due to double counting. The resubmission addressed this issue by setting the retreatment rate to zero, and stating that the retreatment rate was already accounted for in the estimate of patient numbers.

Although the PBAC indicated in March 2020 that the FA uptake rate was likely overestimated (20%–70% over Years 1–6 of listing), the Sponsor retained this uptake rate in the minor resubmission. The Sponsor also retained the assumption of 30% of patients receiving an implant in both eyes.

5.26 The resubmission estimated a net cost to the PBS/RPBS of approximately $0 to <$10M in Year 6 of listing, using effective prices of FA and DEX and published prices of aflibercept and ranibizumab, with a total net cost to the PBS/RPBS of $0 to <$10M over the first 6 years of listing. This is summarised in Table 4, along with the expected patient and prescription numbers. The summary in Table 4 is based on the Excel utilisation spreadsheet accompanying the submission, which does not match the summary tables provided by the Sponsor in the Word document. There were also some minor inconsistencies noted in the spreadsheet.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of FA using effective prices of FA and DEX						
Cost to PBS/RPBS less co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost of displaced drugs to PBS/RPBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to (MBS/DHS/other)	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to (PBS/RPBS/MBS/DHS)	$[redacted][3]	-$[redacted][3]	-$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Sponsor's Excel utilisation spreadsheet: '2. Patients', '3a. Scripts – new' and '7. Net changes – MBS' sheets.
DEX = dexamethasone; DHS = Department of Human Services; DPMQ = dispensed price for maximum quantity; FA = fluocinolone acetonide; MBS = Medicare Benefits; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] Assuming 1.3 scripts per patient per year as estimated by the submission, to account for 30% of patients receiving an implant in both eyes.
The redacted values correspond to the following ranges:
[1]<500
[2]500 to <5,000
[3]$0 million to <$10 million

5.27 As a minor submission, the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangements

5.28 In March 2020, the PBAC noted DEX has a risk sharing arrangement (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). The PBAC advised that FA would be required to join the DEX RSA with no changes to the expenditure caps in order to manage any residual uncertainty regarding the financial estimates. The Sponsor stated in the minor resubmission that they are willing to agree with this condition.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC reaffirmed its previous recommendation from March 2020 for the Authority Required listing of fluocinolone acetonide (FA) for the treatment of diabetic macular oedema (DMO) in patients who are unsuitable for, contraindicated to, or have failed treatment with vascular endothelial growth factor (VEGF) inhibitors. The PBAC made this recommendation on a cost minimisation basis against dexamethasone (DEX), at a dose relativity of 1.3 FA administrations versus 4.11 DEX administrations over 36 months.

6.2 The PBAC noted the input from the Consumer Comments facility on the PBS website, describing a range of benefits with FA including access for suitable patients who are

recalcitrant to other forms of treatment and a reduction in the frequency of intravitreal injections.

6.3 The PBAC recalled that in March 2020, it had considered that a comparison of FA against DEX was appropriate; however, it did not agree that the calculation of the FA price presented in the submission, using a dose relativity of 1 administration FA to 6.48 administrations DEX over 36 months, was appropriate.

6.4 While the Sponsor did not update the clinical claim from the March 2020 submission, that FA is non-inferior to DEX for both comparative effectiveness and safety, they asserted in the resubmission that patients treated with FA had a greater improvement in BCVA compared with DEX, and that clinical and anatomical fluctuations associated with DEX are not seen with FA. The PBAC maintained its view from March 2020 that a claim of non-inferior comparative effectiveness of FA and DEX was reasonable (paragraph 5.5) and that the effectiveness of both DEX and FA was modest (paragraph 6.23, FA PSD, March 2020).

6.5 The Sponsor claimed that the FAME and MEAD trial doses are not representative of Australian and global clinical practice, and the trials should therefore not be used to indicate the equi-effective doses of FA and DEX. The PBAC advised that the equi-effective doses should be derived from an indirect comparison using randomised trials in preference to evidence from nonrandomised studies, in line with PBAC Guidelines. The PBAC considered that non-inferiority had only been reasonably established at the dose frequencies used in the MEAD and FAME trials, and that while it is possible that the pattern of use of FA and DEX in clinical practice is different from the trials, there is a significant risk that FA is inferior to DEX at a ratio of 1 FA:6.48 DEX administrations. The PBAC advised that the original dose relativity from the March 2020 PBAC consideration should be maintained (1.3 FA administrations versus 4.11 DEX administrations over 36 months).

6.6 The cost-minimisation analysis in the resubmission assumed 1 ophthalmologist visit for patients treated with FA and 6.48 visits for patients treated with DEX over 36 months, and specified that FA patients with breakthrough oedema would be treated with anti-VEGF agents. The PBAC reiterated its recommendation from March 2020 that the CMA should only include the cost of drug and the cost of administering the implants. The PBAC noted that it previously considered the number of ophthalmology visits should not be different for FA and DEX (paragraph 6.29, FA PSD, March 2020), and that the proportionate use of concomitant anti-VEGF agents in FA patients was poorly supported (paragraph 6.30, FA PSD, March 2020). The PBAC considered these costs were highly uncertain, not well justified in the March 2020 submission or the resubmission, and should not be included in the CMA.

6.7 The PBAC emphasised that the PBS listing of FA should be cost neutral to the Government, as the Australian population already has access to therapy that is at least as effective and safe.

6.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

7 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.

8 Sponsor's Comment

It is very disappointing that the original PBAC conditional recommendation, and subsequent minor application, has been unsuccessful in achieving a price that is similar to reimbursed prices in Europe and the UK. While the proposed Risk Share terms were acceptable, the ex-manufacture net price offered is less than half the global average reimbursed price for Iluvien. Given the acquisition cost from the drug developer Alimera is greater than the proposed PBS price, and the impact such a low price, if accepted, would have on Alimera's existing reimbursed global pricing, Specialised Therapeutics cannot proceed with Iluvien's listing on the PBS.