7.01 DEXAMETHASONE, implant, 700 µg, Ozurdex®, Allergan.

1 Purpose of Application

1.1 The resubmission requested an Authority Required listing for dexamethasone posterior segment drug delivery system (PS DDS) (referred to in the resubmission as dexamethasone implant) for the treatment of vision impairment due to centre-involving diabetic macular oedema (DME). The first submission for dexamethasone implant was considered at the March 2015 PBAC meeting.

1.2 A coordinated resubmission to MSAC (MSAC Application 1377.1) was lodged by the sponsor in November 2015 for the subsidy of optical coherence tomography (OCT) for the purposes of confirming eligibility for treatment with dexamethasone implant. MSAC had deferred the application for the requested MBS item until such time as PBAC makes a positive recommendation regarding the corresponding PBS listing of the dexamethasone implant. MSAC supported the use of OCT to confirm the presence of macular oedema once a decision has been made to treat (or retreat) with dexamethasone. However, the current resubmission to PBAC specified fluorescein angiography (FA) as the diagnostic tool for determining DME, rather than OCT. The use of OCT to confirm DME in continuing patients was implied in the financial estimates in the submission, although confirmation of DME prior to continuing treatment was not specified in the requested listing for continuing treatment.

2 Requested listing

2.1 The requested listing is presented below with new text proposed by the Secretariat added in italics and suggested deletions are crossed out with strikethrough. The Pre-PBAC Response (p1) offered no objections to these suggestions.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty[a]	Proprietary Name and Manufacturer
DEXAMETHASONE				Ozurdex® Allergan
700 microgram implant, 1	1	1	$[redacted]	

[a] Published price. Note: Special pricing arrangements are proposed.

Authority required General Schedule

PBS Indication:	Diabetic macular oedema (DMO)
Treatment phase:	Initial
Treatment criteria:	Must be treated by an ophthalmologist.

Clinical criteria:	Patient must have visual impairment due to diabetic macular oedema, 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 confirmed by optical coherence tomography; OR* The condition must be ~~diagnosed~~ *confirmed* by fluorescein angiography~~; OR~~ ~~Patient must have a contraindication to fluorescein angiography,~~ *AND* *Patient must be contraindicated, unsuitable for, or have failed prior treatment with vascular endothelial growth factor (VEGF) inhibitors,* AND The treatment must be as monotherapy; *OR* *The treatment must be in combination with laser photocoagulation,* AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must have a pseudophakic lens in the ~~treatment~~ *treated* eye; OR Patient must be scheduled for cataract surgery *in the treated eye*.
Prescriber 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 report or* fluorescein angiogram ~~or alternative method of diagnosis where applicable~~. 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. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised. ~~Where a fluorescein angiogram cannot be performed due to a contraindication as listed in the TGA-approved product information, details of the contraindication must be provided. A copy of the report of an alternative method of diagnosis must be included in the application, for example optical coherence tomography or red free photography.~~

Administrative Advice	Note 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 Prior Written Approval of Complex Drugs Reply Paid 9826 HOBART TAS 7001 Note 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. *Note* *Special Pricing Arrangements apply.*

PBS Indication:	Diabetic macular oedema (DMO)
Treatment phase:	Continuing
Treatment criteria:	Must be treated by an ophthalmologist.
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for the same eye, AND *The condition must be re-confirmed by optical coherence tomography*, AND The treatment must be as monotherapy; *OR* *The treatment must be in combination with laser photocoagulation,* AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must have a pseudophakic lens in the ~~treatment~~ *treated* eye; OR Patient must be scheduled for cataract surgery *in the treated eye*.
Prescriber Instructions	-
Administrative Advice	Note 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). *Note* *Special Pricing Arrangements apply.*

PBS Indication:	Diabetic macular oedema (DMO)
Treatment phase:	Grandfathering
Treatment criteria:	Must be treated by an ophthalmologist.

Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before ~~PBS-listing of treatment~~ *DD MM YYYY [date of PBS listing],* *AND* *Patient must not have received non-PBS-subsidised treatment with this drug for this condition before 1 October 2015,* AND The treatment must be as monotherapy; *OR* *The treatment must be in combination with laser photocoagulation,* AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must have a pseudophakic lens in the ~~treatment~~ *treated* eye; OR Patient must be scheduled for cataract surgery *in the treated eye*.
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought.
Administrative Advice	*Note* *Special Pricing Arrangements apply.*

2.2 Consistent with the previous submission, the sponsor proposed an ex-manufacturer price of $[redacted]. Furthermore, a confidential $[redacted] rebate per prescription was proposed through a special pricing arrangement, making the effective DPMQ price to government $[redacted] (corrected to $[redacted]). Yearly subsidisation caps were also proposed. If the Commonwealth Payment exceeded the subsidisation cap in any year, the sponsor proposed to reimburse the Commonwealth 50% of the amount exceeded.

2.3 The key differences between the proposed listing in the original submission and the resubmission are as follows:

- Treatment with dexamethasone implant must be as monotherapy and must be the sole PBS-subsidised therapy for this condition, as foreshadowed by the PBAC (paragraph 7.3, dexamethasone implant Public Summary Document (PSD), March 2015 PBAC Meeting).
- Discontinuation criteria are no longer specified. The PBAC noted that the discontinuation criteria provided in the original submission (≥15 letter decrease in best corrected visual acuity (BCVA) since the last assessment within 3-6 months of treatment initiation) was larger than a lower non-inferiority limit of -5 letters that was specified for the differences between dexamethasone implant and ranibizumab (paragraph 7.5, dexamethasone implant PSD, March 2015 PBAC Meeting). In the resubmission, the sponsor indicated that it would be willing to consider a continuation criteria for dexamethasone implant, with only those patients achieving a ≥5 letter gain in visual acuity at 3 months following administration permitted to continue treatment. The ESC considered that a stopping rule may be appropriate (see 'Estimated PBS usage and financial implications').
- The diagnostic method for DME has been specified as fluorescein angiography, previously unspecified (paragraph 2.3, dexamethasone implant PSD, March 2015 PBAC Meeting). This method of diagnosis is consistent with both the ranibizumab and aflibercept listings; however, the dexamethasone, aflibercept and ranibizumab trials all used OCT to diagnose DME.
- The definition of visual impairment has changed from a visual acuity of ≤ 6/12 Snellen fraction to a BCVA between 78 and 39 letters based on the early treatment diabetic retinopathy study (ETDRS) chart administered at a distance of

4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment. This is consistent with both the ranibizumab and aflibercept listings.

2.4 While the requested listing restricts usage to patients with pseudophakic lenses, it does not restrict use in patients where vascular endothelial growth factor (VEGF) inhibitors are not the preferred treatment. This may be particularly important if PBAC considers that the dexamethasone implant is not as effective as VEGF inhibitors in the overall pseudophakic population who would otherwise be suitable for treatment with VEGF inhibitors. The Pre-Sub-Committee Response (PSCR) (p1-2) argued that any such restriction would be redundant as clinicians would 'automatically' prescribe the preferred treatment. The ESC did not agree with this argument, and considered it would be necessary to restrict the listing.

2.5 The requested listing also specifies that dexamethasone implant must be as monotherapy, which excludes the concomitant use of laser photocoagulation. This was consistent with the key dexamethasone implant trials, MEAD and BEVORDEX trials. However, use of dexamethasone implant vs VEGF inhibitors may be limited given that a similar restriction was not included in the ranibizumab and aflibercept PBS listings. The ESC noted that there was no evidence provided on the effects of treatment with both dexamethasone implant and laser photocoagulation. The PSCR (p3) clarified that laser photocoagulation is for treating peripheral DME while dexamethasone implant is for treating central DME. The ESC considered that it would be informative for the PBAC to know what proportion of patients had both peripheral and central DME, and whether there would be additional benefit to vision from treating peripheral DME. The Pre-PBAC Response (p2) noted that, in Trial 024, there was no significant difference in the incidence of concurrent laser photocoagulation therapy over the 12 months of the trial between the dexamethasone implant and ranibizumab injection arms. Overall, 6.1% of patients had concomitant laser photocoagulation.

2.6 Listing was sought based on a comparison of the cost of treatment with dexamethasone implant with the costs of treatment with VEGF inhibitors, specifically aflibercept and ranibizumab. This is inappropriate for patients who have a contraindication to or who have failed prior treatment with VEGF inhibitors. Furthermore, it may be inappropriate to compare the cost of dexamethasone implant with VEGF inhibitors for those patients who are determined to be non-compliant with VEGF inhibitors, unless the reduced cost due to non-compliance is also considered.

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

3 Background

3.1 TGA status at time of PBAC consideration: Dexamethasone implant was approved for registration by the TGA for the treatment of diabetic macular oedema (DME) in June 2015.

3.2 The intravitreal implant itself consists of 700 µg dexamethasone in a solid polymer drug delivery system (DDS).

3.3 This was the second consideration by the PBAC of dexamethasone implant for the treatment of vision impairment due to DME in patients who have an artificial lens implant or who are scheduled for cataract surgery. The PBAC considered the original submission at its March 2015 meeting.

3.4 Ranibizumab was recommended by the PBAC for the treatment of vision impairment caused by DME in July 2014. Aflibercept was recommended by the PBAC for the treatment of vision impairment caused by DME in November 2014.

4 Clinical place for the proposed therapy

4.1 DME is a severe complication that can develop at any stage of diabetic retinopathy (DR). DME leads to impaired vision and possibly blindness and impacts the patient's quality of life.

4.2 The dexamethasone implant enables the sustained release of dexamethasone, a potent corticosteroid that suppresses inflammation by inhibiting multiple inflammatory cytokines. This decreases fibrin deposition, capillary leakage, and migration of the inflammatory cells, which in turn reduces macular oedema.

4.3 The resubmission proposed that the dexamethasone implant would be used as an alternative to VEGF inhibitors, for the treatment of DME patients with pseudophakic eyes for whom VEGF inhibition is not the preferred treatment. The resubmission suggested that this population would include those who have a contraindication to or have failed to respond to VEGF inhibitors, or where a patient may be unsuitable for treatment with VEGF inhibitors because of a likelihood of failure to attend the clinic on the number of occasions required. The perceived advantage of using the dexamethasone implant was the reduced requirement for injections. This would benefit patients who were unlikely to be compliant with frequent injections or who may benefit from alternative treatments with longer duration of action (such as in the rural setting), however this should be considered in the context of the potential risk of harm, including:

- the requirement of monitoring for or management of elevated intraocular pressure (IOP) following dexamethasone implant; and
- the inferior treatment effect in terms of visual acuity associated with dexamethasone versus VEGF inhibitors.

4.4 The proposed clinical management algorithm does not indicate the use of dexamethasone to patients where a VEGF inhibitor is not the preferred treatment – the algorithm simply shows dexamethasone as a joint first-line therapy with a VEGF inhibitor. The PSCR (p1) re-affirmed that the proposed place of dexamethasone treatment is for the treatment of a DME patient with a pseudophakic lens for whom a VEGF inhibitor is not the preferred treatment.

4.5 The PBAC agreed that there would be unmet clinical need for patients with DME for whom a VEGF inhibitor is unsuitable for some reason, however, noted that such patients would not generate any cost off-sets from reduced use of VEGF inhibitors.

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

5 Comparator

5.1 The resubmission nominated ranibizumab and aflibercept as the main comparators. Off-label use of bevacizumab was no longer considered as an alternative comparator. Although not explicitly stated in the proposed listing, the resubmission nominated the eligible population as those for whom treatment with VEGF inhibitors is not the preferred treatment option. Therefore, the proposed population contains patients who would otherwise be treated with a VEGF inhibitor in the absence of an alternative, as well as those who have a contraindication to or who have failed to respond to a VEGF inhibitor. Ranibizumab and aflibercept are appropriate comparators for patients suitable for treatment with a VEGF inhibitor and may be appropriate comparators for patients for whom a VEGF inhibitor is not the preferred treatment (poor compliance due to the frequency of VEGF inhibitor injections), or those who are unlikely to attend the clinic on the number of occasions required. "No treatment" is the appropriate comparator for patients who either have a contraindication to or have failed to respond to a VEGF inhibitor. The PSCR (p2) suggested that patients who have a contraindication to, or who have failed, a VEGF inhibitor, are likely to be a minority of patients who would be treated in practice. The ESC did not find evidence to quantify the size of this minority.

5.2 The ESC noted that intravitreal triamcinolone, provided through the TGA's Special Access Scheme, may also be a relevant comparator because, although it is not PBS-listed, it is a closer pharmacological analogue than any of the PBS-listed comparators.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical need and positioning of this therapy, outlined the comparative effectiveness and safety of dexamethasone implant, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was not informative as it did not add substantively to the evidence presented in the submission.

Consumer comments

6.4 The PBAC noted and welcomed the input from individuals (2), health care professionals (15), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dexamethasone implant including less frequent injections compared with VEGF inhibitors. This was considered particularly beneficial for patients in rural and remote areas, especially the Aboriginal and Torres Strait Islander populations. The benefits of less frequent injections were described in terms of compliance with treatment, patient acceptability and reduced financial burden.

6.5 The PBAC noted the advice received from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) and the Macular Disease Foundation of Australia (the Foundation) clarifying the likely use of dexamethasone implant in clinical practice. The PBAC specifically noted the RANZCO advice that the use of dexamethasone implant has proved a safe and effective treatment for centre-involving DME, with its alternative mechanism of action from VEGF inhibitors making it a useful addition to existing ophthalmic treatments. The PBAC noted the Foundation's advice that dexamethasone implant provides a safe and effective treatment option for patients with DME who have a contraindication to, who have failed treatment with, or who are otherwise unsuitable for VEGF inhibitors. The Foundation described how dexamethasone implant, with its lower frequency of injections, reduced the burden of care on patients, their carers, and the public hospital system. The Foundation also highlighted that patients currently using off-label intravitreal triamcinolone are expected to switch to dexamethasone implant if it is PBS listed, due to its improved safety profile. The PBAC noted that these organisations' advices were supportive of the evidence provided in the submission.

Clinical trials

6.6 No additional direct trials comparing dexamethasone implant with ranibizumab injection were identified by the resubmission.

6.7 The resubmission presented indirect comparisons of dexamethasone implant *versus* aflibercept injection based on eight trials involving either dexamethasone implant or aflibercept injection for treatment of visual impairment due to DME:

- one trial (Trial 024) comparing dexamethasone implant with ranibizumab injection;
- one trial (BEVORDEX) comparing dexamethasone implant with bevacizumab injection;
- two trials (MEAD trials) comparing dexamethasone implant with sham (placebo);
- one trial (Protocol T) comparing the three VEGF inhibitors, aflibercept injection, ranibizumab injection and bevacizumab injection; and
- three trials (VIVID, VISTA and DA VINCI) comparing aflibercept with laser photocoagulation.

6.8 Details of the trials presented in the resubmission are provided in Table 1.

Table 1: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Dexamethasone implant trials		
Trial 024	Clinical Study Report 206207-024: A multicentre, open-label, randomized trial comparing the efficacy and safety of 700µg dexamethasone posterior segment drug delivery system (DEX PS DDS) to ranibizumab in patients with diabetic macular edema.	July 2014
BEVORDEX	Gillies MC., Lim LL., Campain AE., *et al*. A multicentre randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study.	*Ophthalmology* 2014; 121(12):2473-81
	Gillies MC., Lim LL., Campain AE., *et al*. BEVORDEX - A multicentre randomized clinical trial of intravitreal dexamethasone versus intravitreal bevacizumab for persistent diabetic macular edema (abstract).	2015 ARVO Annual Meeting
MEAD (Trials 010 and 011)	Clinical Study Report 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 edema.	May 2013
	Clinical Study Report 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 edema.	May 2013
	Boyer DS., Yoon YH., Belfort R., *et al*. (2014). Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema.	*Ophthalmology* 2014; 121(10):1904-14
Aflibercept injection trials		
VIVID/VISTA	Korobelnik JF., Do DV., Schmidt-Erfurth, U. *et al*. Intravitreal aflibercept for diabetic macular edema.	*Ophthalmology* 2014, 121(11):2247-54.
DA VINCI	Do DV., Schmidt-Erfurth, U., Gonzalez, VH., *et al.* The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema.	*Ophthalmology* 2011; 118(9): 1819-26
	Do DV., Nguyen QD, Boyer D., *et al*. 2012. One-year outcomes of the DA VINCI study of VEGF trap-eye in eyes with diabetic macular edema.	*Ophthalmology* 2012; 119:1658-65
Protocol T	DRCR Network, Wells JA., Glassman AR, *et al*. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema.	*New England Journal of Medicine* 2015; 372(13): 1193-203

DRCR = Diabetic Retinopathy Clinical Research
Source: Table B-9, pp60-61 of the resubmission

6.9 All trials, except for Protocol T, were included in the previous dexamethasone implant or aflibercept submissions and have been considered by the PBAC.

6.10 The key features of the randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N[a]	Design/ duration	Risk of bias[b]	Patient population[a]	Outcome	Use in modelled evaluation
Dexamethasone implant *vs* ranibizumab injection						
Trial 024	116	R, SB, MC 12 mths	High	Subgroup of patients with pseudophakic lens with vision impairment due to DME (ITT: patients with vision impairment due to DME)	BCVA change in ETDRS letters from baseline at Month 12	The number of injections in Year 1
Dexamethasone implant *vs* bevacizumab injection						
BEVORDEX	26	R, SB, MC 12 mths	High	Subgroup of patients with pseudophakic lens with vision impairment due to DME (ITT: patients with vision impairment due to DME)	BCVA change in ETDRS letters from baseline at Month 12	No
Dexamethasone implant *vs* sham						
MEAD trials	187	R, DB, MC 36 mths	High	Subgroup of patients with pseudophakic lens with vision impairment due to DME (ITT: patients with vision impairment due to DME)	BCVA change in ETDRS letters from baseline at Month 12	The number of injections beyond Year 1
Aflibercept injection *vs* ranibizumab injection *vs* bevacizumab injection						
Protocol T	620	R, DB, MC 24 mths	High	Subgroup of patients with vision impairment due to DME (ITT: patients with vision impairment due to DME)	BCVA change in ETDRS letters from baseline at Month 12	No
Aflibercept injection *vs* laser photocoagulation						
VIVID	267	R, DB, MC 12 mths	High	Patients with vision impairment due to DME	BCVA change in ETDRS letters from baseline at Month 12	No
VISTA	305	R, DB, MC 12 mths	High			
DA VINCI	86	R, DB, MC 12 mths	High			
Meta-analysis	658	Included VIVID, VISTA and DA VINCI; assessed BCVA				No

BCVA = best corrected visual acuity; DB = blinded to patients and outcome assessor but not to treating investigators; ETDRS = Early Treatment Diabetic Retinopathy Study; ITT = intention-to-treat; MC = multi-centre; R = randomised; SB = blinded to outcome assessor but not to participants or investigators

[a] Number of patients included for the indirect comparisons of change in BCVA from baseline. For dexamethasone trials, DME patients without a pseudophakic lens were excluded from analysis of BCVA change, but included for safety analysis. Patients who did not receive the recommended treatment regimens (*eg* patients in the 2Q4 (2mg aflibercept every 4 weeks) arms in VIVID, VISTA and DA VINCI) were excluded for both effectiveness and safety analysis.

[b] Refers to bias associated with indirect comparisons between dexamethasone implant and aflibercept injection. There is a high risk of bias associated with the indirect comparisons as the trials involved were not exchangeable.

Source: compiled during the evaluation

6.11 Adjusted indirect comparisons were performed using three common references: ranibizumab injection, bevacizumab injection and sham/laser. The interventions in the so-called 'common reference groups' were either different treatments (eg sham injection in MEAD trials vs laser photocoagulation in VIVID/VISTA and DA VINCI) or with different retreatment criteria and/or dosage of one study drug (eg ranibizumab arms in Trial 024 vs Protocol T; bevacizumab arms in BEVORDEX vs Protocol T). In addition, indirect comparisons of the primary efficacy outcome, ie mean change in BCVA from baseline, were performed between the pseudophakic subgroups from the dexamethasone trials and the overall DME populations from the aflibercept trials.

Given the major exchangeability concerns outlined above, along with other observed heterogeneities among the included trials, common reference-based indirect comparisons presented in the resubmission cannot reliably determine the comparative effectiveness and safety for dexamethasone implant versus aflibercept injection.

6.12 The non-inferiority margin proposed in the resubmission was -5 letters change in BCVA from baseline at Month 12. When the PBAC considered the claim of superior comparative effectiveness of ranibizumab injection versus laser photocoagulation in the ranibizumab submission at the March 2013 meeting, the PBAC "recalled it had previously accepted that an improvement in visual acuity of 10 letters represented a clinically important result. The PBAC was uncertain as to whether an improvement in visual acuity of 5-6 letters could also be considered clinically important. The PBAC agreed that an increase of 5 letters or more might represent a clinically meaningful difference for some patients in treatment of DME, but the clinical importance will also depend on the baseline visual acuity of each eye" (p5, ranibizumab injection PSD, March 2013 PBAC meeting). The PBAC indicated that "a mean BCVA change of -5 letters in the lower bound non-inferiority limit was probably reasonable" when it considered the previous dexamethasone implant submission (paragraph 7.5, dexamethasone implant PSD, March 2015 PBAC meeting).

Comparative effectiveness

6.13 Key results of indirect comparisons of dexamethasone implant and aflibercept injection in terms of BCVA change from baseline at Month 12 are presented in Table 3.

Table 3: Results of change in BCVA from baseline at Month 12 across the randomised trials

Trial ID	Trial of dexamethasone implant (pseudophakic subgroup)			Trial of aflibercept injection (overall DME population)			Indirect comparison[c] AD (letters) [95% CI]
	AD (letters)[a] [95% CI]	Dexamethasone implant N Mean (SD)	Common comparator N Mean (SD)	Common comparator N Mean (SD)	Aflibercept injection N Mean (SD)	AD (letters)[b] [95% CI]	
Ranibizumab as the common comparator							
Trial 024	[redacted]	N=54 [redacted]	N=62 [redacted]	–	–	–	[redacted]
Protocol T	–	–	–	N=206 11.2 (9.4)	N=208 13.3 (11.1)	2.1 [0.1, 4.1]	
Bevacizumab as the common comparator							
BEVORDEX	2.7 [-7.5, 12.9]	N=16 10.4 (14.7)	N=10 7.7 (11.6)	–	–	–	**-0.8 [-11.2, 9.6]**
Protocol T	–	–	–	N=206 9.7 (10.1)	N=208 13.3 (11.1)	3.5 [1.4, 5.7]	
Sham/laser as the common reference							
MEAD trials	4.7 [2.6, 6.8]	N=86 6.5 (8.1)	N=101 1.7 (7.1)	–	–	–	**-5.4 [-8.1, -2.8]**
VIVID	–	–	–	N=132 1.2 (10.6)	N=135 10.7 (9.3)	9.5 [7.1, 11.9]	
VISTA	–	–	–	N=154 0.2 (12.5)	N=151 10.7 (8.2)	10.5 [8.1, 12.9]	
DA VINCI	–	–	–	N=44 -1.3 (2.0)	N=42 9.7 (14.6)	11.0 [6.6, 15.5]	
Pooled AD[d] (letters) [95% CI]	–	–	–	10.1 [8.6, 11.7] χ^2: 0.51, df: 2, p-value: 0.776			

AD = absolute difference; CI = confidence interval; DME = diabetic macular oedema; SD = standard deviation

[a] Dexamethasone implant *vs* common comparator. A positive result indicates treatment effect favouring dexamethasone implant.

[b] Aflibercept injection *vs* common comparator. A positive result indicates treatment effect favouring aflibercept injection.

[c] Dexamethasone implant *vs* aflibercept injection. A negative result indicates treatment effect against dexamethasone implant.

[d] Pooled using random effects model. The test of heterogeneity was conducted during the evaluation.

Source: Table B-21 to Table B-23, p103-105 of the resubmission

6.14 The results of indirect comparisons, using ranibizumab injection, bevacizumab injection or sham/laser as the common reference, consistently indicated a lower improvement in BCVA in patients receiving dexamethasone implant compared with those treated with aflibercept injection. For all indirect comparisons, the lower bounds of the 95% confidence intervals (CIs) (-7.3 to -11.2 letters) were below the nominated non-inferiority margin of -5 letters. The differences reached statistical significance in the indirect comparisons with ranibizumab injection or sham/laser as the common reference. The results of the indirect comparisons should be interpreted with caution given the lack of exchangeability of the trials, which is particularly noticeable when comparing the change from baseline in BCVA across reference arms (eg ranibizumab arms: [redacted] letters in Trial 024 versus 11.2 letters in Protocol T). The PSCR (p2) recognised that dexamethasone implant may be inferior to aflibercept injection in a population in whom an intensive VEGF inhibitor regimen poses no issues. The ESC agreed with this view.

6.15 The resubmission indicated that one of the challenges facing DME patients and care providers in clinical practice is the frequent administration of VEGF inhibitor

intravitreal injections and, thus, the potential for poor compliance. Based on results from observational studies on the use of ranibizumab for treatment of DME, the resubmission concluded that the mean number of ranibizumab injections in clinical practice was less than that reported in the clinical trials and was associated with a reduced clinical benefit in visual acuity. Treatment frequency of ranibizumab and change in visual acuity are both likely to be affected by multiple factors, such as treatment compliance, the treatment protocol specified in a clinical study/trial, and patients' history of previous VEGF inhibitor treatment. The ranibizumab retreatment criteria in two of the observational studies (Pearce et al 2014 and Patrao et al 2015) differed from those in Trial 024. Information on the treatment regimens in the remaining DME studies is absent. In addition, data on prior use of VEGF inhibitors in the DME studies were not provided. The direction of causation for the association between lower number of injections and smaller average letter gain over a year is unknown. Overall, poor treatment compliance with a VEGF inhibitor in clinical practice, although plausible, has not been adequately supported by the evidence presented in the resubmission. The resubmission also did not provide convincing evidence indicating improved treatment compliance with dexamethasone implant in a real-world setting. Dose-response curves (where dose is determined by frequency) were not provided for any of the medicines. Therefore, it cannot be reliably determined whether or to what extent the difference, if any, in the treatment compliance with dexamethasone implant versus VEGF inhibitors would affect the comparative treatment effect.

Comparative harms

6.16 Indirect comparisons of the safety results between dexamethasone implant and aflibercept injection were based on overall DME patients who received at least one dose of the study drug, due to the insufficient safety data for the pseudophakic subgroup from the included trials. Interpretation of the safety results, particularly the risk of ocular adverse events likely to be associated with development of cataracts, should consider that listing is proposed for patients with an artificial lens (pseudophakic eye) and thus may have limited applicability. The other major concern is the lack of exchangeability between the trial sets, particularly the varying treatments in the common reference groups.

6.17 Results of all indirect comparisons indicated a higher rate of elevated IOP with dexamethasone implant compared to aflibercept injection (indirect relative risks (RRs): 4.31 [1.29, 14.43], 2.47 [0.62, 9.29] and 6.16 [1.88, 20.20], using ranibizumab, bevacizumab and sham/laser, respectively, as the common reference). In comparison with aflibercept injection, dexamethasone implant was associated with a significantly higher incidence of overall ocular adverse events (indirect RR: 1.58 [1.28, 1.95] and vitreous floaters (indirect RR: 7.61 [1.63, 35.47]), using sham/laser and ranibizumab, respectively, as the common reference. The risk for conjunctival haemorrhage was numerically greater in patients receiving dexamethasone implant than those in the aflibercept injection arms, when compared with the results from Trial 024 and Protocol T using ranibizumab as the common reference (indirect RR: 1.43 [0.70, 2.91]). Results from indirect comparisons, although lacking exchangeability, suggest an inferior safety profile of dexamethasone implant compared with a VEGF inhibitor for some important adverse events.

Benefits/harms

6.18 Given the lack of comparative evidence from head-to-head trials and the major concerns regarding the indirect comparisons of clinical studies with exchangeability issues, a summary table of benefits and harms for dexamethasone implant relative to aflibercept injection was not formulated as it would likely be misleading.

Clinical claim

6.19 The resubmission described dexamethasone implant as non-inferior to ranibizumab injection, but acknowledged that dexamethasone implant might be inferior to aflibercept injection, in terms of effectiveness in DME patients with pseudophakic eyes (or eyes scheduled for cataract surgery). The resubmission described dexamethasone implant as inferior to ranibizumab injection and aflibercept injection in terms of safety.

6.20 The claim of non-inferior comparative effectiveness of dexamethasone implant versus ranibizumab injection was previously rejected by the PBAC based on the direct Trial 024. No new direct evidence was presented in the current resubmission which could change this conclusion. The inferiority claim of dexamethasone implant compared with aflibercept injection in terms of effectiveness is appropriate. The claim of inferior safety profile of dexamethasone implant versus the PBS-listed VEGF inhibitors, ie ranibizumab and aflibercept, has been supported by the clinical evidence presented in the previous submission and in the current resubmission.

6.21 The resubmission maintained that dexamethasone implant is non-inferior to ranibizumab and aflibercept injections in a subgroup of patients for whom a VEGF inhibitor is not the preferred option. This clinical claim has not been justified. VEGF inhibitors are not the appropriate comparator for dexamethasone implant for patients who have a contraindication to or have failed a VEGF inhibitor. In patients for whom a VEGF inhibitor is not preferred due to concerns surrounding compliance, a VEGF inhibitor may be an appropriate comparator. However, the resubmission did not conduct any formal direct or indirect comparisons of dexamethasone implant versus ranibizumab or aflibercept in the non-compliant patients to determine the comparative treatment effect of these drugs.

6.22 Consistent with its previous finding, the PBAC considered that the claim of non-inferior comparative effectiveness to ranibizumab was not adequately supported by the data. The PBAC considered that the claim of inferior comparative effectiveness to aflibercept injection was reasonable. Overall, the PBAC concluded from the evidence provided that dexamethasone implant is less effective than either ranibizumab or aflibercept injection.

6.23 The PBAC considered that the claim of inferior comparative safety between dexamethasone and ranibizumab or aflibercept injections was reasonable.

Economic analysis

6.24 The resubmission compared the costs of treatment with dexamethasone implant with the costs of treatment with ranibizumab and aflibercept injections. Costs of managing elevated IOP, associated with dexamethasone implant, were included in the

resubmission. The cost of administration of each interventional drug was also included. The approach presented in the resubmission is identical to that presented in the previous submission.

6.25 Consistent with the original submission, the resubmission presented the "equi-effective doses" of dexamethasone versus comparator drugs as the numbers of injections of dexamethasone implant 700 µg versus ranibizumab 0.5 mg, and versus aflibercept 2 mg in a given time period. These numbers of injections used in the resubmission for each time period are summarised in Table 4.

Table 4: The number of injections used when comparing the costs associated with dexamethasone implant with the costs associated with ranibizumab and aflibercept

Treatment period	Dexamethasone implant 700 µg	Ranibizumab injection 0.5 mg	Aflibercept injection 2 mg
Months 1-12	2.76	8.60	8.60[a]
Months 12-23	1.92	3.7	3.7[a]
Months 24-36	1.80	2.7	2.7[a]
Total Months 1-36	6.48	15.0	15.0 [a]

[a] The resubmission assumed that the number of administrations for aflibercept is the same as that for ranibizumab.
Source: Table C.2-3, p150 of the resubmission

6.26 The relative numbers of injections between dexamethasone implant and ranibizumab remained unchanged from the original submission. At the March 2015 meeting, the PBAC considered that the approach taken by the previous submission in estimating the "equi-effective" frequency of retreatments of dexamethasone implants compared with VEGF inhibitor injections in a given time period (rather than "equi-effective doses") was unreliable due to problems with the sample size, exchangeability and applicability of the data sources (paragraph 7.9, dexamethasone implant PSD, March 2015 PBAC meeting).

6.27 The resubmission assumed identical numbers of injection per year across aflibercept and ranibizumab. This assumption appeared reasonable, being consistent with previous PBAC advice on the relative injection frequency across VEGF inhibitor injections for treatment of DME, when the PBAC considered the aflibercept submission at the November 2014 meeting (aflibercept PSD, November 2014 PBAC meeting). However, due to the concern surrounding the estimation of the relative treatment frequencies between dexamethasone implant and ranibizumab, the estimated numbers of injections of dexamethasone implant versus aflibercept were also subject to uncertainty.

6.28 The resubmission estimated the costs of administration of each drug, specialist visit and OCT use based on a survey of five ophthalmologists in the base case analysis. The PBAC previously considered that this was inappropriate (paragraph 6.30, dexamethasone implant PSD, March 2015 PBAC Meeting). The MBS schedule fee or proposed schedule fee (for OCT) should have been based on the Manual of Resource Items and their Associated Costs for use in submissions to the PBAC involving economic evaluation (December 2009). Using the surveyed average cost per administration, per specialist visit and per OCT introduced uncertainty given the very small number of ophthalmologists and biased the results favouring dexamethasone implant. The resubmission provided sensitivity analyses using the MBS schedule fee.

6.29 The resubmission presented an additional sensitivity analysis that calculated the cost-effectiveness of dexamethasone implant vs ranibizumab/aflibercept injection, using the results of the cost-minimisation analysis above and treatment effect (BCVA letters gained) from the indirect comparison. Results should be interpreted as a cost saving per letter lost, given the inferior treatment effect of dexamethasone implant compared to ranibizumab and aflibercept. These results should be interpreted with caution given the concerns regarding the estimation of the relative frequency of injections and concerns regarding exchangeability of patient populations in the indirect comparison.

6.30 The resubmission's cost-minimisation analysis indicated that the dexamethasone implant would result in cost savings compared with the VEGF inhibitors. During the evaluation, the total costs for the administration of each drug used the MBS schedule fees only and the results indicated that the savings from the substitution of VEGF inhibitors by dexamethasone implant were overestimated in the resubmission. Further, the effective price of ranibizumab is unknown to the resubmission and thus the cost comparison is not accurate.

6.31 The results of the cost-effectiveness analyses were interpreted with caution due to concerns regarding the estimation of the relative frequency of injections, exchangeability of patient populations used in the indirect comparison, and inclusion of additional patient expenses which are not necessarily justified.

6.32 The PBAC considered that the resubmission's cost-minimisation approach was not justified because the claim of non-inferiority of dexamethasone implant verses ranibizumab or aflibercept injection was not supported by the clinical evidence presented in the original submission or the resubmission.

6.33 Furthermore, based on the conclusion that dexamethasone implant is associated with increased costs compared with to ranibizumab and aflibercept injection due to the need to manage increased intraocular pressure (IOP), and as included in the economic evaluation in the resubmission, the PBAC considered that it would be appropriate to correspondingly reduce the price of dexamethasone implant compared to the cheapest PBS-listed VEGF inhibitor.

6.34 The PBAC re-affirmed its previous view that the estimates of the relative frequency of retreatments of dexamethasone implants compared with VEGF inhibitor injections in a given time period are unreliable due to problems with the sample size, exchangeability and applicability of the data sources. Nonetheless, the PBAC recognised the unmet clinical need for this therapy among patients who have a contraindication to a VEGF inhibitor, or where a VEGF inhibitor is unsuitable for reasons relating to frequency of administration. The PBAC noted that the resubmission estimated that, over a 36-month period, dexamethasone implant would be administered 6.48 times compared to 15.0 times for ranibizumab or aflibercept (see Table 4). The PBAC therefore considered that a pragmatic way forward would be to price dexamethasone implant lower than the cost of the cheapest PBS-listed VEGF inhibitor treatment over 36 months (see Table 4). The PBAC noted that retreatment frequencies declined in subsequent years, but considered this approach remained reasonable in view of the greater estimated reduction in retreatment frequency for VEGF inhibitors than for dexamethasone implant over years 2 and 3. The PBAC further considered that, given the positioning of a substantial proportion of

dexamethasone for use in patients who have a contraindication to, are unsuitable for, or have failed prior treatment with VEGF inhibitors, the pragmatic way forward was to exclude the MBS costs of administration in the calculation of the price.

6.35 The PBAC also considered that the results of the additional sensitivity analysis of the cost-effectiveness of dexamethasone implant versus ranibizumab/aflibercept injection in terms of cost-saving per letter loss in BCVA were both difficult to interpret and unreliable as they were based on indirect comparisons of clinical trials lacking exchangeability. Rather, the PBAC advised that, consistent with its pragmatic approach, a price reduction in the order of [redacted]% to [redacted]% would be required to satisfactorily account for the inferior safety and effectiveness of dexamethasone implant compared with the cheapest PBS-listed VEGF inhibitor. The alternative approach would be to consider a cost-effectiveness analysis or cost-consequences analysis comparing a reduced cost of using dexamethasone in place of this comparator against the set of reduced health outcomes to formally address this difficult value judgement.

Drug cost/patient/year

6.36 The cost of dexamethasone implant/eye was estimated to be $[redacted] for the first year (assuming 3 implants required), and $[redacted] for years 2 and 3 (assuming 2 implants required).

Estimated PBS usage & financial implications

6.37 This resubmission was not considered by DUSC. The resubmission used a combination of epidemiological and market share approaches to estimate the extent of use and the financial implications associated with the PBS listing of dexamethasone implant for the treatment of DME. The resubmission assumed that patients likely to be treated with dexamethasone implant would otherwise receive ranibizumab/aflibercept injection. Given that the resubmission claimed the clinical place of dexamethasone implant is among those who are unsuitable for treatment with VEGF inhibitors (patients who have a contraindication to, or have failed to respond to a VEGF inhibitor; or where a patient may be unsuitable for treatment with a VEGF inhibitor because of a likelihood of failure to attend the clinic on the number of occasions), it is reasonable to expect some growth in the current market. The ESC noted that the submission and the PSCR (p1) claimed that the clinical place for dexamethasone implant is in treating those patients who have a contraindication or are unwilling to undertake treatment with currently listed VEGF inhibitors. At the same time, the submission claimed that uptake of dexamethasone will result in cost off-sets of greater than $20 – $30 million per year by reducing the use of VEGF inhibitors. The ESC considered that this was incompatible with the likely consequences of the proposed niche market. The estimated use and financial implications as estimated in the resubmission are summarised below in Table 5. The Pre-PBAC Response (p2) acknowledged the uncertainty with respect to the update of dexamethasone implant in Australia.

Table 5: Estimated use and financial implications

Estimate	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to the PBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to the MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to other government health budgets	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net cost to government health budgets	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Assuming: 1) 2.76 scripts per patient in 1st year of treatment, 1.9 scripts per patient in 2nd year of treatment and 1.8 scripts per patient in 3rd – 5th years of treatment; and 2) 56% patients with bilateral DME.
Source: Table E8 and E-9, and E-19 Section E of the resubmission

6.38 Results from sensitivity analyses indicated that the net financial implications for government health budgets were most sensitive to the uptake rate. When the uptake of dexamethasone implant dropped from 17% (base case) to 10%, the net cost savings to the government decreased by around 40%. The ESC noted that the sensitivity analysis including a stopping rule for the 43% of patients who would not gain at least 5 letters of visual acuity at 3 months reduced savings to Government by 40%. The ESC suggested that inclusion of discontinuation criteria in the restriction may be appropriate. The PBAC raised no objection to omitting the previously proposed stopping rule.

6.39 At year 1, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $20 – $30 million. At year 5, the estimated number of patients was 10,000 – 50,000 and the estimated net saving to the PBS would be $10 – $20 million.

Financial Management – Risk Sharing Arrangements

6.40 The sponsor offered a rebate of $[redacted] per prescription through special pricing arrangement and proposed a risk sharing agreement, offering a [redacted]% rebate for utilisation beyond an agreed subsidisation cap. The subsidisation cap is based on the resubmission's financial and utilisation estimates of dexamethasone implant.

6.41 The PBAC recommended that the department negotiate a Risk Share Arrangement with the sponsor due to the uncertainty in the uptake of this therapy. The PBAC recommended that a [redacted]% rebate should apply for use beyond subsidisation caps based on the utilisation estimates presented in the submission.

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

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required listing of dexamethasone implant, on the basis of inferior effectiveness and inferior safety compared to ranibizumab and aflibercept and thus on appropriately adjusted estimates of cost-effectiveness.

7.2 The PBAC recognised an unmet clinical need for this therapy among patients who have a contraindication to, or have failed to respond to a VEGF inhibitor, or where a VEGF inhibitor is unsuitable due to frequency of administration. However, the PBAC also noted that patients with DME for whom a VEGF inhibitor is unsuitable for some reason would not generate any cost off-sets from reduced use of VEGF inhibitors.

7.3 The PBAC recommended the PBS restriction as suggested by the Secretariat, including omitting reference to a stopping rule as proposed in the previous submission. The PBAC noted that as Complex Authority Required item, the Department of Human Services (DHS) would be responsible for the administration of the written authority approvals. The DHS 'Diabetic Macular Oedema (DMO) - PBS Supporting Information Form' would require amendments for use with this listing. The PBAC therefore noted that the restriction is considered to be complex and may be influenced by the outcome of the MSAC deliberations regarding OCT.

7.4 The PBAC considered that ranibizumab and aflibercept are appropriate comparators for patients suitable for treatment with a VEGF inhibitor and for patients for whom a VEGF inhibitor is not the preferred treatment (due to patient preference or logistical reasons relating to the frequency of VEGF inhibitor injections). The PBAC considered that "no treatment" is the appropriate comparator for patients who either have a contraindication to or have failed to respond to a VEGF inhibitor, or for whom a VEGF inhibitor is otherwise unsuitable.

7.5 The PBAC noted that the resubmission presented indirect comparisons of dexamethasone implant versus aflibercept injection based on eight trials involving either dexamethasone implant or aflibercept injection for treatment of visual impairment due to DME. The PBAC had concerns around the exchangeability of the trials, primarily due to the differences in the study populations included for analysis of change in best corrected visual acuity from baseline and in the interventions of the common reference groups.

7.6 Consistent with its previous finding, the PBAC considered that the claim of non-inferior comparative effectiveness to ranibizumab was not adequately supported by the data. The PBAC considered that the claim of inferior comparative effectiveness to aflibercept injection was reasonable. Overall, the PBAC concluded from the evidence provided that dexamethasone implant is less effective than either ranibizumab or aflibercept injection.

7.7 The PBAC considered that the claim of inferior comparative safety between dexamethasone and ranibizumab/aflibercept injections was reasonable.

7.8 The PBAC considered that the resubmission's cost-minimisation approach was not justified because the claim of non-inferiority of dexamethasone implant verses ranibizumab or aflibercept injection was not supported by the clinical evidence presented in the original submission or the resubmission. Thus the approach taken did not form a suitable basis for PBAC consideration.

7.9 Given that the clinical place of dexamethasone implant is among those who are unsuitable for treatment with VEGF inhibitors, the PBAC considered that it would be reasonable to expect some growth in the current market, rather than assuming substitution for VEGF inhibitors as the basis for claiming overall cost savings. The

PBAC also noted that the financial estimates were most sensitive to the uptake rate. Therefore, PBAC recommended that a Risk Share Arrangement be agreed between the sponsor and the Department of Health due to this uncertainty regarding uptake rates. The PBAC recommended that a [redacted]% rebate should apply for use beyond subsidisation caps based on the utilisation estimates presented in the submission.

7.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that dexamethasone implant should not be treated as interchangeable on an individual patient basis with any other medicine listed in the PBS.

7.11 The PBAC advised that dexamethasone implant is not suitable for prescribing by nurse practitioners, as it must prescribed by an ophthalmologist.

7.12 The PBAC recommended that the Early Supply Rule should apply.

7.13 The re-submission is not eligible for an Independent Review, because the PBAC made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item: Restriction to be finalised

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Allergan welcomes the recommendation by the PBAC. PBS listing of dexamethasone implant will expand the options available to ophthalmologists to individualise treatment based on patients' circumstances.