

5.07 DEXAMETHASONE 700 µg implant; Ozurdex®; Allergan Australia Pty Limited

1 Purpose of Application

- 1.1 The submission requested an Authority Required (streamlined) listing for dexamethasone posterior segment drug delivery system (PS DDS) (referred to in the submission as dexamethasone implant) for the treatment of vision impairment due to centre-involving diabetic macular oedema (DME).
- 1.2 A concurrent submission was received by the Medical Services Advisory Committee (MSAC) that requested an MBS listing for optical coherence tomography (OCT) for retinal assessment, in the presence of DME with vision impairment, to enable access to treatment with dexamethasone implant. The sponsor proposed that if OCT was not considered by MSAC to be a cost-effective additional diagnostic service, the dexamethasone implant submission should still be considered for a PBS listing because OCT is not used to predict the treatment effect of dexamethasone implant.

2 Requested listing

- 2.1 The requested listing is presented below.

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

*Published price. Note: Special pricing arrangements are proposed.

Condition	Visual impairment
Restriction	Authority Required (streamlined)
Treatment phase	Initial and continuing
Treatment criteria	Must be treated by an ophthalmologist. Must be discontinued if the patient experiences a ≥ 15 letter decrease in best corrected visual acuity (BCVA) since the last assessment within 3-6 months of last treatment.
Clinical criteria	The condition must be due to diabetic macular oedema. The condition must have resulted in reduced visual acuity of $\leq 6/12$ Snellen fraction. Patient must have a pseudophakic lens in the treatment eye or be scheduled for cataract surgery.
Population criteria	Patient must be an adult.

- 2.2 The submission proposed an ex-manufacturer price of \$█████ and an \$█████ rebate per prescription through special pricing arrangements, making the effective dispensed price for maximum quantity (DPMQ) \$█████. The submission also proposed yearly subsidisation caps. If the Commonwealth payment exceeds the subsidisation cap in any year, 50% of the amount exceeded would be reimbursed to the Commonwealth Government.
- 2.3 It was noted in the requested restriction that:
- the DME diagnostic method was not specified;
 - the range of vision impairment eligible for dexamethasone (reduced visual acuity (VA) \leq 6/12 Snellen fraction) was broader than the inclusion criterion in Trial 024 (approximately 6/12-6/60 Snellen fraction) and would allow patients with severe vision loss to access treatment;
 - the concomitant use of vascular endothelial growth factor (VEGF) inhibitors was not precluded during treatment with dexamethasone implant. Literature identified during the evaluation included one ongoing trial (the DRCR.net Protocol U trial) assessing the use of ranibizumab with dexamethasone implant in patients with persistent macular oedema and pseudophakic eyes (completion date: January 2016). The Pre-Sub-Committee Response (PSCR) advised that reimbursement was not being sought for the concomitant use of dexamethasone implant and VEGF inhibitors. The PSCR suggested the restriction could include ‘treatment must be the sole PBS-subsidised therapy for this condition’;
 - treatment must be discontinued if the patient experiences a \geq 15 letter decrease in BCVA since the last assessment within 3-6 months of last treatment. This is larger than a lower non-inferiority limit of -5 letters that was specified for the difference between dexamethasone implant and ranibizumab, in terms of mean BCVA change from baseline.
- 2.4 Listing was sought based on a comparison of the cost of treatment with dexamethasone implant with the costs of treatment with VEGF inhibitors.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive TGA Delegate’s summary was available.
- 3.2 This was the first 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. Ranibizumab was recommended by PBAC for the treatment of vision impairment caused by DME in July 2014. The ESC noted that aflibercept also received a positive PBAC recommendation for DME in November 2014.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

4 Clinical place for the proposed therapy

- 4.1 DME is a severe complication that can develop at any stage of diabetic retinopathy. 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 intravitreal implant itself consists of 700µg dexamethasone in a solid polymer drug delivery system (DDS). The polymer DDS contains poly (D,L-lactide-co-glycolide) PLGA biodegradable polymer matrix (preservative free).
- 4.4 The submission proposed that the dexamethasone implant would be used as an alternative to VEGF inhibitors, for the treatment of DME patients with pseudophakic eyes. The perceived advantage of using the dexamethasone implant was a reduced frequency of 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).

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

5 Comparator

- 5.1 The submission nominated ranibizumab as the main comparator and off-label bevacizumab as an additional comparator. The ESC considered the comparators were reasonable, although noted that aflibercept could now be considered as an additional comparator.

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 specialist clinician presenting at the hearing focussed on the clinical need for dexamethasone in patients with diabetic macular oedema and the benefits in using it. The clinician advised that even though VEGF inhibitors are available in the market, dexamethasone provides as alternative treatment option wherein the sustained release action reduces the need for frequent medical appointments. The clinician advised that patients with DME suitable for dexamethasone implant would have a pseudophakic lens, or be scheduled for cataract surgery, or who experience difficulty attending frequent appointments (in remote locations). The clinician reiterated that the safety issues with the use of dexamethasone implant particularly elevated intra-ocular pressure were mild to moderate but predictable reactions which could be managed with topical eye drops.

- 6.2 The PBAC sought clarification on two issues:
- Requested PBS population – whether dexamethasone should be limited to pseudophakic patients or a broader DME population, noting that the EMA had also approved second-line use after VEGF inhibitors. The clinician advised that the initial TGA application was based on US data from a large trial without any subgroup population. However during evaluation, the indication was narrowed down to pseudophakic patients.
 - Frequency of re-treatment – the clinician advised that the trial data support re-treatment with the implant every four to five months and therefore averaging three implants per year.
- 6.3 The PBAC considered that the hearing was informative.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (2), health care professionals (5), and organisations (3) via the Consumer Comments facility in the PBS website. The comments described a range of benefits of treatment with dexamethasone including:
- less medical visits because of less frequent injections;
 - reduced risks to eyesight by reducing treatment procedures and subsequent risks associated with procedures;
 - better compliance; and
 - greater independence due to vision improvement.

Clinical trials

- 6.5 The submission was based on two non-inferiority trials comparing dexamethasone implant with VEGF inhibitors in patients with DME – one comparing dexamethasone implant with ranibizumab (Trial 024: N=363) and one comparing dexamethasone implant with bevacizumab (Trial BEVORDEX: N=88). Both trials had a median follow-up of one year. BEVORDEX was a 2-year trial, but only a 12-month interim analysis was available.
- 6.6 The non-inferiority limit proposed in the submission was 5 letters change in BCVA from baseline at Month 12. The PBAC previously 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 would also depend on the baseline visual acuity of each eye (Ranibizumab Public Summary Document, PBAC meeting March 2013). The ESC considered that if a <5 letters change from baseline at Month 12 is considered non-inferior, then the pooled results of the MEAD trials suggest that dexamethasone may not be superior to sham injection. In the pooled analysis over 12 months, the difference in mean change from baseline in BCVA was 3.1 letters (95% CI: 1.9, 4.2) for dexamethasone 700 µg over sham, and 3.2 letters (95% CI: 2.0, 4.3) for dexamethasone 350 µg over sham.
- 6.7 The submission also included two supportive trials comparing dexamethasone implant with sham (placebo) (n=701) in patients with DME over three years of follow-up – Trials 010 and 011, also called the MEAD trials.
- 6.8 The pseudophakic subgroups in Trial 024 (n=116) and the MEAD trials (n=187) were pre-specified, but stratified randomisation was not undertaken. It was unclear

whether the pseudophakic subgroup in the BEVORDEX trial (n=26) was pre-specified. The PSCR stated that it was pre-specified, but that randomisation was not stratified for this subgroup.

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

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
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 oedema.	31 July 2014
BEVORDEX	Gillies, M. et al. A multicentre randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular oedema.	Ophthalmology 2014;121(12):2473–2481.
Supplementary randomised trials		
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 oedema.	20 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 oedema.	20 May 2013
	Boyer, D.S. et al. (2014). Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular oedema.	Ophthalmology 2014;121(10):1904–1914.

Source: Table B.2.2, p7 of Section B of the submission.

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

Key features of the included evidence

Trial	N#	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in economic evaluation
Dexamethasone implant vs. VEGF inhibitors - ranibizumab (Trial 024) or bevacizumab (Trial BEVORDEX)						
Trial 024	116	R, SB, MC 12 months	Unclear*	Patients with pseudophakic lens with vision impairment due to DME	BCVA mean change (letters) from baseline at Month 12	The dose and number of injections
BEVORDEX	26	R, SB, MC 12 months	High**			
Meta-analysis		Included Trials 024 and BEVORDEX; assessed BCVA				
Dexamethasone implant vs. sham						
MEAD	187	R, DB, MC 36 months	High**	Patients with pseudophakic lens with vision impairment due to DME	BCVA mean change (letters) from baseline at Month 12	The number of injections beyond Year 1

SB = blinded to outcome assessor but not to participants or investigators; DB=double blind; BCVA = best corrected visual acuity; R = randomised; MC = multi-centre; DME = diabetic macular oedema.

N represents number of eyes or number of patients as the best seeing eye per patient was chosen as the study eye.

* The pseudophakic subgroup in Trial 024 was pre-specified, but pseudophakic eye was not a stratification factor in randomisation. Both participants and investigators were not blinded to treatment allocation, although the outcome assessors were blinded. It is unclear whether blinding of outcome assessors would necessarily address any systematic differences between trial arms in terms of the frequency and methods of assessment by non-blinded investigators.

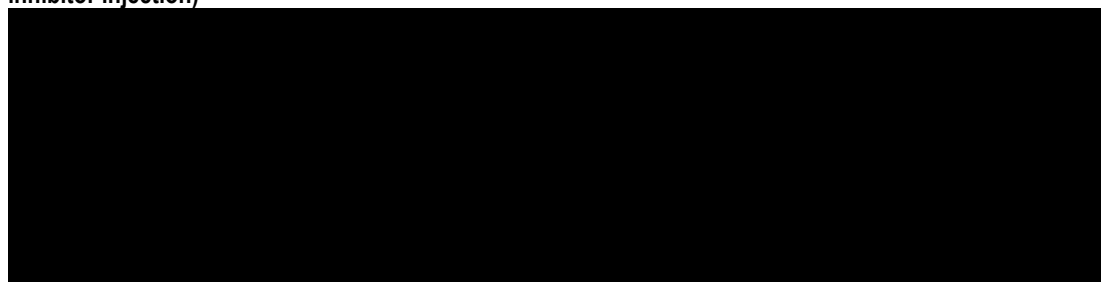
** About 30% of the ITT eyes were pseudophakic at baseline in all the included trials. Baseline characteristics for this subgroup were not available for the BEVORDEX and MEAD trials, so confounding due to incomparable baseline characteristics cannot be ruled out.

Source: compiled during the evaluation.

Comparative effectiveness

6.11 Meta-analyses of the 024 and BEVORDEX trials were presented in the submission for both the ITT and pseudophakic subgroup populations. The results are summarised in the figures below.

Meta-analysis – Mean BCVA change from baseline in ITT population (dexamethasone implant vs. VEGF inhibitor injection)



n represents number of eyes or number of patients as the best seeing eye per patient was chosen as the study eye.

Source: Figure B.6.1, p58 of Section B of the submission.

Meta-analysis – Mean BCVA change from baseline in pseudophakic population (dexamethasone implant vs. VEGF inhibitor injection)



Source: Figure B.6.2, p58 of Section B of the submission.

- 6.12 The ITT results suggested a statistically significant difference in average BCVA change from baseline at Month 12, favouring VEGF inhibitors over dexamethasone implant. Comparing the lower bound of the 95% CI with the non-inferiority limit of -5 letters, the dexamethasone implant appears clinically non-inferior to VEGF inhibitors.
- 6.13 In the pseudophakic patient subgroup of Trial 024, the average BCVA improvement from baseline associated with the dexamethasone implant (■■■■ letters) was non-inferior to ranibizumab injection (■■■■ letters) using a non-inferiority limit of -5 letters. The relative mean BCVA change from baseline favoured ranibizumab although this difference was not statistically significant (95% CI ■■■■■■■■■■). The lower bound of ■■■■ letters, when rounded to whole letters, was the same as the non-inferiority limit.
- 6.14 The meta-analysis of the findings from the pseudophakic subgroup was difficult to interpret, with significant heterogeneity in terms of both direction and magnitude of treatment effect in the two trials included in meta-analysis. The results favoured dexamethasone implant over VEGF inhibitor therapy in BEVORDEX but the converse was true in Trial 024.
- 6.15 The pseudophakic subgroup results from the BEVORDEX trial were not convincing due to the small number of eyes assessed, and lack of reported baseline data to judge whether patients in the two treatment arms were sufficiently similar to mitigate significant confounding.

Comparative harms

- 6.16 Data from the overall ITT safety population and the pseudophakic subgroup are summarised below. The sample size of eyes in the BEVORDEX trial was too small to assess any uncommon adverse events (AEs).

Treatment-related ocular AEs in Trial 024 and the BEVORDEX trial

Safety, Trial 024	Dexamethasone implant, n (%)	Ranibizumab injection, n (%)	RR (95% CI)	ARD (95% CI)
N (safety population)	181	182		
Overall AEs	██████	██████	██████	██████
Increased IOP ^a	██████	██████	██████	██████
Conjunctival haemorrhage	██████	██████	██████	██████
N (pseudophakic population)	54	62		
Overall AEs	██████	██████	██████	██████
Increased IOP ^a	██████	██████	██████	██████
Conjunctival haemorrhage	██████	██████	██████	██████
Safety, BEVORDEX trial^b	Dexamethasone implant, n (%)	Bevacizumab injection, n (%)	RR (95% CI)	ARD (95% CI)
N (safety population)	46	42		
Increased IOP (≥5 mmHg)	21 (45.7)	8 (19.0)	2.40 (1.25, 4.59)	0.27(0.07, 0.46)

n represents number of eyes or number of patients as the best seeing eye per patient was chosen as the study eye.

^a Not defined in Table 12-4, pp79-80 of 024 clinical study report

^b Safety data for the pseudophakic population were not available

NC=Not calculable; AE = adverse event; IOP = intraocular pressure; RR = relative risk; ARD = absolute risk difference.

Source: Constructed during the evaluation, based on Table B.6-13, p79, Section B of the submission and Table 3, p6 Gilles MC et al.

- 6.17 Treatment-related ocular AEs occurred in █████% of Trial 024 participants in the pseudophakic population. The incidence of treatment-related ocular AEs in the trial eye was higher in the dexamethasone implant arm (█████%) compared with the ranibizumab injection arm (█████%), giving a risk difference of █████% (95% CI: █████%, █████%).
- 6.18 That is, for every 100 patients treated with dexamethasone implant rather than ranibizumab, █████ additional patients will experience a treatment-related adverse ocular event. The incidence of increased IOP and conjunctival haemorrhage was also statistically significantly higher in the dexamethasone implant arm compared to the ranibizumab injection arm.

Benefits/harms

- 6.19 A summary of the comparative benefits and harms for dexamethasone implant versus ranibizumab or bevacizumab intravitreal injection is presented in the table below. The evidence suggested an inferior safety profile associated with dexamethasone implant relative to ranibizumab or bevacizumab.

Summary of comparative benefits and harms for dexamethasone and VEGF inhibitors

Benefits in the ITT population							
Continuous outcome I: change from baseline BCVA in letters							
	Dex			VEGF inhibitors			Mean difference ^{a,b} Dex vs. VEGF inhibitors (95% CI)
	n	Mean BCVA at baseline (SD)	Mean Δ baseline BCVA (SD)	n	Mean BCVA at baseline (SD)	Mean Δ baseline BCVA (SD)	
Trial 024	181						
BEVORDEX	46	NR	5.6 (16.3)	42	NR	8.9 (8.8)	-3.30 (-8.71, 2.11)
Harms							
	Dex	VEGF inhibitor	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)	
				Dex	VEGF inhibitor		
Trial 024 in the pseudophakic subgroup ^d							
Overall treatment related ocular AEs							
Increased IOP ^c							
Conjunctival haemorrhage							
Trial BEVORDEX ^d							
Increased IOP (≥5 mmHg)	21/46 (45.70%)	8/42 (19.00%)	2.40 (1.25, 4.59)	45.70	19.00	0.27 (0.07, 0.46)	

^a Median duration of follow-up of 12 months.

^b Estimated difference of change from baseline, 95% CI and p-values for treatment comparison is based on the least-squares means from a 2-way ANOVA model with the treatment and baseline BCVA categories (<=49 letters vs. >=50 letters) as main effects using the Type III sum of squares.

^c Not defined in Table 12-4, pp79-80 of 024 clinical study report.

^d Safety data of BEVORDEX trial were reported for overall safety population, safety data for the pseudophakic population were not available.

Dex = dexamethasone; VEGF = vascular endothelial growth factor; RD = risk difference; RR = risk ratio; CI = confidence interval; SD = standard deviation; NR = not reported; NC = not calculable.

Source: Compiled during the evaluation.

- 6.20 On the basis of the 024 trial presented by the submission, the comparison of dexamethasone implant and ranibizumab over 12 months follow-up resulted in:
- no statistically significant difference in the mean change of BCVA from baseline
 - for every 100 pseudophakic patients treated with dexamethasone implant compared with those treated with ranibizumab:
 - approximately 30 additional patients would experience a treatment-related ocular adverse event
 - approximately 41 additional patients would experience elevated intraocular pressure (IOP)
 - approximately 14 additional patients would experience conjunctival haemorrhage.
- 6.21 On the basis of the BEVORDEX trial presented by the submission, the comparison of dexamethasone implant and bevacizumab over 12 months follow-up resulted in:
- no statistically significant difference in the mean change of BCVA from baseline
 - for every 100 patients treated with dexamethasone implant compared with those treated with bevacizumab, approximately 27 additional patients would experience elevated IOP.

Clinical claim

- 6.22 The submission described the dexamethasone implant as being non-inferior in terms of comparative effectiveness and safety relative to either ranibizumab or bevacizumab.
- 6.23 This claim was not adequately supported:
- In terms of the effectiveness of dexamethasone implant versus ranibizumab, the claim of non-inferiority for relative mean BCVA change from baseline was equivocal; the lower 95% confidence interval limit of █████ letters, when rounded to whole letters, was the same as the pre-specified non-inferiority limit of -5 letters. Importantly, the safety analyses indicated a potentially inferior safety profile associated with the dexamethasone implant, in terms of elevated IOP and conjunctival haemorrhage. The submission noted these dexamethasone AEs need to be 'balanced' with potential systemic side effects of VEGF-inhibitor. However, the submission did not provide the incidence of these dexamethasone AEs in the pseudophakic population; and
 - In terms of the effectiveness of dexamethasone implant versus bevacizumab (BEVORDEX trial), the results of the pseudophakic subgroup analysis were uncertain due to the small size of the subgroup and lack of baseline data to judge the impact of any potential confounding. Safety data for the pseudophakic subgroup were also lacking. However, the overall safety analyses suggested a potentially inferior safety profile associated with dexamethasone implant, at least for elevated IOP. This was consistent with findings from Trial 024.
- 6.24 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.25 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.26 The submission compared the costs of treatment with dexamethasone implant with the costs of treatment with ranibizumab, bevacizumab and aflibercept. Costs of managing adverse event of elevated IOP, associated with dexamethasone implant, were included in the submission. The cost of administration of each interventional drug was also included.
- 6.27 The submission did not present the equi-effective doses of dexamethasone versus comparator drugs. Instead, the submission estimated the equi-effective numbers of injections of dexamethasone implant 700 µg versus ranibizumab 0.5 mg, and versus bevacizumab 1.25 mg. The estimates presented in the submission are summarised below.

The equi-effective number of injections assumed when comparing the costs associated with dexamethasone implant with the costs associated with ranibizumab, bevacizumab and aflibercept

Treatment period	Dexamethasone implant	Ranibizumab injection	Bevacizumab injection	Aflibercept injection
Months 1-12 (Year 1)	2.76	█	8.60	12.0
Months 12-23 (Year 2)	1.92	3.7	3.7	3.7
Months 24-36 (Year 3)	1.80	2.7	2.7	2.7

Source: Table C.3.3, p10 of Section C of the submission.

- 6.28 The numbers of injections estimated above were considered unreliable. The number of injections for Years 2 and 3 were derived from single arms extracted from different trials. The comparison was therefore indirect by nature and it was unknown whether the patient characteristics were comparable across these sources of evidence. The dosing frequencies of ranibizumab were sourced from Trial 024 (for Year 1 of treatment) and the RESTORE extension study (for Years 2 and 3). In trial 024, approximately █% of patients were VEGF inhibitor experienced (pseudophakic patients) dexamethasone arm (█%) and ranibizumab arm (█%). However, this proportion in clinical practice is uncertain. Such patients may require fewer VEGF inhibitor injections. Thus the difference in the number of treatments between dexamethasone implant and ranibizumab injection in Year 1 of comparison could have been overestimated. The PSCR argued that although the dosing frequencies were sourced from the ranibizumab trials, patient characteristics in the MEAD trial were similar to patients in the RESTORE trial. The PSCR claimed that all scenarios in the sensitivity analyses indicate dexamethasone implant remained a cost-saving.
- 6.29 Furthermore, derivation of the number of dexamethasone implants for Years 2 and 3 of the cost analysis was based on small numbers of pseudophakic patients in the dexamethasone implant arm of the MEAD trials (N=44 and 35, respectively) and may not be reliable. The numbers of injections for ranibizumab in Years 2 and 3 were based on all patients who enrolled in the RESTORE extension trial, in which there were no data for the pseudophakic subgroup. The applicability of these data to the proposed PBS population remains unreliable. The submission assumed that the number of injections of bevacizumab and aflibercept in the second and third years of treatment would be similar to that observed for ranibizumab injection in the RESTORE extension study, without providing any justification for this assumption.
- 6.30 The submission 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 estimate of OCT use based on a survey of five ophthalmologists was considered unreliable. 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 the major submissions to the PBAC (December 2009). Using the surveyed average cost per administration, per specialist visit, and per OCT made the estimated costs less reliable given the very small number of ophthalmologists and biased the results favouring dexamethasone implant. The submission provided sensitivity analyses using the MBS schedule fee. The PSCR maintained that the approach in the submission conforms to the PBAC Guidelines wherein the economic evaluation considered all contributions to the costs of healthcare resources including those paid for by patients.

6.31 The submission’s economic 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 were re-calculated using the MBS schedule fees, which reduced the extent savings. The effective price of ranibizumab was also unknown to the submission which also affects the accuracy of the submission’s estimate.

Drug cost/patient/year

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

Estimated PBS usage & financial implications

6.33 This submission was not considered by DUSC. The submission 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 submission assumed that patients likely to be treated with dexamethasone implant would otherwise receive ranibizumab injection. This assumption appeared reasonable, as it was expected that a vast majority of patients currently receiving off-label bevacizumab would switch to the PBS-listed ranibizumab prior to dexamethasone implant being listed. The estimated use and financial implications as estimated in the submission are summarised below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]
Net cost to MBS	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]	[\$ [REDACTED]]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	[\$ [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 E.2-3, p9 and Table E.5-5, p17 of Section E of the main submission.

6.34 The redacted table above shows that the uptake of dexamethasone implant is expected to be less than 10,000 patients per year and would result in net savings to the PBS/RPBS/MBS of \$10 - \$20 million in years 1 to 5.

- 6.35 The cost savings associated with the use of dexamethasone implant could vary if the uptake rate and the size of the eligible population are not as predicted in the submission. In addition, the estimated cost savings to the PBS would not be realised if: 1) dexamethasone implant is to be used in addition to ranibizumab injection; 2) the number of patients seeking active treatment increases following the proposed listing (market growth) due to the claimed advantage of reduced treatment frequency associated with dexamethasone implant compared with VEGF inhibitors; and 3) the proportion of VEGF inhibitor-experienced patients in the target population is higher than that in Trial 024 (about █%).
- 6.36 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 █% (base case) to 10%, the net cost savings to the government decreased by around 40%.

Financial Management – Risk Sharing Arrangements

- 6.37 The submission proposed an ex-manufacturer price of \$█ and an \$█ rebate per prescription through special pricing arrangements, resulting in an effective DPMQ of \$█. The submission also proposed yearly subsidisation caps based on the submission's financial and utilisation estimates of dexamethasone implant. If the Commonwealth payment exceeds the subsidisation cap in any year, 50% of the amount exceeded would be reimbursed to the Commonwealth Government.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the submission to list dexamethasone implant for the treatment of diabetic macular oedema (DME) on the basis that the evidence presented did not conclusively establish clinical non-inferiority of dexamethasone implant compared with ranibizumab and bevacizumab.
- 7.2 The PBAC considered that the eligible patient population and clinical place of dexamethasone implant were not well-defined, noting that the broadest population, as reflected in the FDA approval and original proposal for TGA approval, would be for "adult patients with diabetic macular edema". Although the intended PBS population was clarified as being "patients with vision impairment due to centre-involving DME who also have pseudophakic lens or who are also scheduled for cataract surgery", the PBAC noted that the TGA delegate and other regulatory agencies also contemplated second-line use by patients who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy.
- 7.3 For the treatment of DME patients with pseudophakic eyes, the submission proposed that VEGF inhibitors were appropriate comparators to dexamethasone implant. However, the PBAC noted that should dexamethasone use extend to second-line after VEGF inhibitors, these medicines would not be appropriate comparators. The PBAC foreshadowed that any PBS restriction of dexamethasone implant would include the criterion that 'treatment must be the sole PBS-subsidised therapy for this condition'.

- 7.4 For the intended PBS population, the PBAC therefore accepted ranibizumab and bevacizumab were appropriate comparators. The PBAC agreed with ESC that aflibercept could now also be considered as a comparator, noting it received a positive PBAC recommendation for DME in November 2014.
- 7.5 The PBAC noted the results of the meta-analyses comparing dexamethasone implant against ranibizumab (Trial 024) and against bevacizumab (BEVORDEX) in the ITT population and pseudophakic subgroup. The PBAC noted the issues raised by ESC regarding the use of the lower bound of the 95% CI non-inferiority margin. The PBAC considered that a mean BCVA change of -5 letters in the lower bound non-inferiority limit was probably reasonable, however the PBAC considered that the point estimates in the meta-analysis in the ITT population suggest dexamethasone implant is less effective than VEGF inhibitors. The PBAC considered that the meta-analysis in the pseudophakic subgroup was more difficult to interpret the results because of significant heterogeneity in both direction and magnitude of treatment effect in the two trials.
- 7.6 The PBAC recalled the ranibizumab submission considered in July 2014. The PBAC noted that the DRCR.net randomised trial compared ranibizumab (plus prompt or deferred laser) with triamcinolone (plus prompt laser). The PBAC noted that associated publications (Jonas JB et al. *Br J Ophthalmol* 2005;89:321-6 and Shah CP. *Evidence-Based Ophthalmol* 2008;10:29-30) have indicated that the short-term improvements in visual acuity in DME with intravitreal triamcinolone acetonide are not sustained. Given that dexamethasone belongs to the same pharmacological class as triamcinolone, the PBAC considered the long-term durability of response for dexamethasone would need to be established.
- 7.7 Overall, the PBAC considered that the claim of non-inferiority in terms of comparative effectiveness had not been adequately supported in the submission, and that dexamethasone implant may be less effective than VEGF inhibitors.
- 7.8 In terms of comparative safety, the PBAC noted that dexamethasone implant was associated with statistically significant increases in intra-ocular pressure (IOP) and increased conjunctival haemorrhage compared to ranibizumab in pseudophakic patients (Trial 024). The sponsor in its Pre-PBAC Response acknowledged this, but reiterated that the increases in IOP were transient and readily managed with topical eye drops. The PBAC agreed that IOP and conjunctival haemorrhage might be easy to treat, however they should not be dismissed in the overall consideration of comparative safety. Overall, the PBAC did not accept the non-inferiority claim in terms of comparative safety against ranibizumab.
- 7.9 The PBAC did not accept the cost-minimisation analysis in the submission given that the clinical evidence did not clearly support non-inferiority. The PBAC also considered that the approach taken by the submission in estimating the equi-effective frequency of re-treatments 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. The PBAC agreed with the issues outlined above in paragraphs [6.28 to 6.29]. The PBAC noted that the TGA delegate had also queried the frequency of dexamethasone implant re-treatment, noting that “[t]he

protocol in the pivotal RCTs was for a 6-monthly dosing interval, but there is some evidence that more frequent dosing might be beneficial”.

- 7.10 The PBAC noted the likely financial savings to the PBS to be reduced from those estimated in the submission due to doubts about the claimed advantage of reduced treatment frequency associated with dexamethasone implant compared with VEGF inhibitors, and the need for the ranibizumab and/or aflibercept recommendations to be implemented first before any savings could be achieved. The PBAC considered that financial implications could be relied on with more confidence if the estimated frequency of dexamethasone implants for Years 2 and 3 were to be based on a more robust source.
- 7.11 The PBAC considered that any future major resubmission maintaining a non-inferiority claim against ranibizumab, aflibercept (now a second main comparator) and bevacizumab would need to have a stronger basis than the current submission. This may take the form of new data and/or further justification for why dexamethasone implant’s effectiveness and safety should be non-inferior compared to ranibizumab, aflibercept and bevacizumab. The PBAC also considered that the long-term durability of response for dexamethasone implant would need to be established, as discussed above in paragraph [7.6], and the long-term frequency of re-treatment with dexamethasone implant would need to be determined, as discussed above in paragraph [7.9].
- 7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor’s Comment

Allergan are committed to addressing the concerns raised by the PBAC in order to ensure patients with visual impairment due to diabetic macular oedema have access to dexamethasone implant.