6.04 RANIBIZUMAB, 2.3 mg/0.23 mL, 0.23 mL vial and 1.65 mg/0.165 mL, pre-filled syringe Lucentis®, Novartis Australia Pty Ltd.

1 Purpose of application

1.1 The submission requested an extension to the current Authority required listing for ranibizumab to include treatment, by an ophthalmologist, of patients with subfoveal choroidal neovascularisation (CNV) secondary to pathologic myopia (PM). This is the first request for PBAC consideration of ranibizumab for this population.

1.2 A similar submission requesting extension of the current listing for ranibizumab to include treatment of CNV caused by conditions other than age-related macular degeneration (AMD) or PM was also lodged for consideration at the March 2018 PBAC meeting.

1.3 The submission was based on a cost-utility analysis of ranibizumab compared with verteporfin photodynamic therapy (vPDT) in patients with CNV secondary to PM.

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

Component	Description
Population	Patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia. The requested restriction in Section 1.4 of the submission is for subfoveal CNV due to PM.
Intervention	Ranibizumab solution for intravitreal injection.
Comparator	Verteporfin photodynamic therapy (vPDT).
Outcomes	Mean average change in best corrected visual acuity (BCVA), quality of life, and safety.
Clinical claim	In patients with choroidal neovascularisation secondary to pathologic myopia, ranibizumab is superior to vPDT in terms of efficacy and quality of life, and non-inferior to vPDT in terms of safety.

vPDT = verteporfin photodynamic therapy
Source: Table 1.1-1, p26 of the submission.

2 Requested listing

2.1 The submission requested an Authority Required listing for ranibizumab for the treatment of patients with subfoveal CNV secondary to PM.

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
RANIBIZUMAB				Lucentis	Novartis Pharmaceuticals Australia Pty Ltd
2.3 mg/0.23 mL injection, 0.23 mL vial	1	2	$1149.44 $[redacted]*		
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe	1	2	$1149.44 $[redacted]*		

* effective prices

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Subfoveal choroidal neovascularisation
PBS Indication:	Subfoveal choroidal neovascularisation
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ *Authority Required - Telephone* ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist *or in consultation with an ophthalmologist*.
Clinical criteria:	The condition must be due to pathologic myopia *(PM)* AND The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography AND The treatment must be the sole PBS-subsidised therapy for this condition.
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 Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and* *c) a copy of the optical coherence tomography or fluorescein angiogram report.* *A telephone application must be made following submission by facsimile of a copy of a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.*
Administrative Advice	*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.* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001* *Special Pricing Arrangements apply.* *Pharmaceutical benefits that have the form ranibizumab 0.165 mL injection syringe and pharmaceutical benefits that have the form ranibizumab 0.23 mL injection vial are equivalent for the purposes of substitution.*

2.3 CNV lesions are classified according to their location relative to the fovea. The fovea is the centre of the macula and is the area of the eye that provides the sharpest vision. CNV lesions that are directly under the fovea are described as subfoveal. Juxtafoveal and extrafoveal lesions are located adjacent to and away from the fovea, respectively.

2.4 The submission requested a PBS listing of ranibizumab for the treatment of subfoveal CNV secondary to PM. The TGA indication is for the treatment of visual impairment due to CNV secondary to PM, regardless of the location of the lesion.

2.5 The submission stated the focus of the submission was subfoveal CNV lesions, because it is these lesions that lead to the visual impairment for which ranibizumab is a registered treatment, and that juxtafoveal and extrafoveal lesions can be successfully treated by laser photocoagulation. Approximately 30% of patients in the two key trials had juxtafoveal or extrafoveal CNV lesions. The ESC agreed with the proposal to limit PBS listing to subfoveal CNV as this would effectively target the highest risk group for more extensive vision loss.

2.6 The submission proposed that ranibizumab usage in subfoveal CNV due to PM be listed at the same published and effective price as for the treatment of subfoveal CNV due to AMD, and should be incorporated into the risk sharing arrangement (RSA) negotiated to cover that population. (See Financial Management – Risk Sharing Arrangements, below for more detail).

2.7 The submission also requested a grandfather clause for patients currently receiving compassionate supply of ranibizumab through the sponsor.

2.8 The current MBS item descriptor for optical coherence tomography (OCT) (MBS item 11219) does not include determining whether the requirements for access to initial treatment with ranibizumab for CNV secondary to PM under the PBS are fulfilled. The submission stated that the sponsor would seek approval from MSAC to have the MBS item descriptor for OCT broadened to include this population in the event of approval of ranibizumab for listing on the PBS, and the Department has since arranged to coordinate more effectively across the two committees.

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

3 Background

Registration status

3.1 Ranibizumab was TGA registered in 2014 for the treatment of visual impairment due to CNV secondary to PM.

Previous PBAC consideration

3.2 Ranibizumab has not been previously considered by the PBAC for subfoveal CNV secondary to PM. Ranibizumab is currently listed on the PBS for the treatment of subfoveal CNV due to AMD, diabetic macular oedema (DME), central retinal vein occlusion with macular oedema and branch retinal vein occlusion with macular oedema.

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

4 Population and disease

4.1 Pathologic myopia is a severe form of myopia, or short-sightedness, associated with an abnormal elongation of the eyeball and high myopia. CNV is a vision-threatening complication of PM and is characterised by the growth of pathologic new blood vessels from the choriocapillaris through a break in the Bruch's membrane into the space under the retinal pigment epithelium or retina. Without treatment, the prognosis is poor, with over 90% of affected eyes likely to have a progressive and irreversible deterioration of vision leading to blindness within 10 years.

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

5 Comparator

5.1 The submission nominated vPDT as the main comparator, on the basis that verteporfin photodynamic therapy (vPDT) is the only subsidised therapy for the treatment of CNV due to PM (PDT is subsidised on the MBS), and that the PM maculopathy is being interpreted by some prescribers as being due to AMD in order to gain access to PBS-subsidised verteporfin.

5.2 The cost-effectiveness of verteporfin for the treatment of CNV due to PM has not been accepted by the PBAC. In its consideration of the November 2005 submission requesting listing of verteporfin for subfoveal CNV due to AMD and other macular diseases (including CNV due to PM), the PBAC did not recommend verteporfin for the treatment of CNV due to other macular diseases. This was because of the unacceptable incremental cost per extra quality-adjusted life year (QALY) gained of more than $200,000 (Section 12, verteporfin Public Summary Document (PSD), November 2005 PBAC meeting). Although the sponsor argued the selection of an active comparator was a conservative approach (Pre-Sub-Committee response (PSCR)), the clinical effectiveness of verteporfin was also not supported by the PBAC in November 2005; which noted that, for patients with CNV due to PM, the statistically significant reduction in risk of visual loss at 12 months did not persist at 24 months (Section 12, verteporfin PSD, November 2005 PBAC meeting). The PBAC considered that the economic evaluation presented in the submission, comparing ranibizumab and vPDT was not useful in informing the cost-effectiveness of ranibizumab for the treatment of CNV due to PM.

5.3 MBS statistics suggest that the use of vPDT in current clinical practice is minimal. In the financial estimates, the submission assumed that currently, [redacted], with roughly equal proportions receiving aflibercept and ranibizumab.

5.4 Currently, no medicines are listed on the PBS for the treatment of subfoveal CNV due to PM. Ranibizumab and aflibercept, which are both VEGF inhibitors, are TGA approved for the treatment of visual impairment due to CNV secondary to PM; verteporfin is registered for the treatment of patients with subfoveal CNV caused by macular disease[i], which includes CNV due to PM.

5.5 In the absence of an alternative treatment that has been determined to be cost-effective for this indication, the ESC considered that no treatment (sham injection) was the most appropriate comparator for assessing clinical and cost-effectiveness of ranibizumab for the treatment of CNV due to PM. The PBAC agreed with the ESC that sham injection (as a proxy for no treatment) is the most appropriate comparator to inform its decision.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from the Royal Australian and New Zealand College of Ophthalmologists in support of a listing of ranibizumab for the treatment of patients with CNV due to PM.

Clinical trials

6.3 The submission was based on two head-to-head randomised trials comparing ranibizumab to vPDT in patients with CNV due to PM: RADIANCE and BRILLIANCE. The two trials were similar in design. Both were multi-centre, randomised double-masked (masking was maintained by the use of a ranibizumab sham treatment and a vPDT sham treatment), controlled trials comparing two different dosing regimens of ranibizumab versus vPDT. Patients were randomised in a 2:2:1 ratio to one of the following three treatment arms:

[i] The TGA approved indication for verteporfin is for the treatment of patients with predominantly classic or occult subfoveal CNV due to AMD, or with subfoveal CNV caused by other macular diseases.

Group I: ranibizumab 0.5 mg guided by visual acuity (VA) stabilisation criteria.

- ranibizumab 0.5 mg on day 1 and Month 1 (1 month ± 7 days), and thereafter as needed, guided by VA stabilisation criteria (RADIANCE N=106, BRILLIANCE N=182),

Group II: ranibizumab 0.5 mg guided by disease activity criteria.

- ranibizumab 0.5 mg on day 1, and thereafter as needed, guided by disease activity criteria based on anatomical changes seen in fluorescein angiography (FA) or OCT (RADIANCE N=116, BRILLIANCE N=184), or

Group III: vPDT

- vPDT on day 1. From Month 3 (3 months ± 7 days), the investigator had the option to treat the patient's disease activity with ranibizumab 0.5 mg, vPDT (performed as per label), or both (RADIANCE N=55, BRILLIANCE N=91).

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RADIANCE	Clinical Study Report: A 12-month, Phase III, randomized, double-masked, multi-center, active-controlled study to evaluate efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab vs verteporfin PDT in patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia.	November 2012
	Wolf S, Balciuniene VJ, Laganovska G et al. RADIANCE: A randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia.	*Ophthalmology* 2014; 121(3): 682-92
BRILLIANCE	Clinical Study Report: A 12-month, Phase III, randomized, double-masked, multi-center, active-controlled study to evaluate efficacy and safety of two individualized regimens of 0.5 mg ranibizumab vs verteporfin PDT in patients with visual impairment due to choroidal neovascularisation secondary to pathologic myopia.	March 2017

Source: Table 2.2-1, p42 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Ranibizumab vs. vPDT						
RADIANCE	277	R, DB/ 3 mths[a]	Low	CNV secondary to PM	Mean average BCVA change from baseline to month 1 through month 3 of the study eye	Used (only data from all patients in Group II and 15 patients in Group III are used)
BRILLIANCE	457	R, DB/ 3 mths[a]	Low	CNV secondary to PM	As above	Not used

BCVA = best corrected visual acuity; CNV = choroidal neovascularisation; DB=double blind; PM = pathologic myopia; R = randomised.
[a] Duration of follow-up for the primary outcome, prior to the allowance of treatment switching for patients randomised to vPDT. The total duration of follow-up in the trial was 12 months.
Source: Sections 2.3 and 2.4, pp43-58 of the submission.

6.6 Both trials included adult patients with CNV due to PM, with the presence of high myopia, and one of the following lesion types in the study eye: subfoveal, juxtafoveal

or extrafoveal with involvement of the central macular area, or margin of the optic disk with involvement of the central macular area.

6.7 One eye was selected as the study eye. If both eyes were eligible, the eye with the worse visual acuity (VA), as assessed at visit 1, was selected for study treatment. For the fellow eye, standard of care or other treatments for PM or other diseases was permitted at any time. The outcomes of the trials were assessed with the study eye.

6.8 Subfoveal CNV lesions were found in 68.5% of patients in RADIANCE and [redacted]% of patients in BRILLIANCE. Approximately 40% of patients in RADIANCE and [redacted]% of patients in BRILLIANCE were Asian. There was no clear evidence of treatment effect modification by race (Caucasian vs Asian) in RADIANCE.

6.9 Both trials excluded patients who had previously received intraocular treatment with any VEGF inhibitors or vPDT in the study eye, or had pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye. Therefore, at baseline, the trial populations were largely treatment-naïve in regard to prior treatment for CNV in the study eye. As a consequence, the submission provided limited comparative data for treatment-experienced patients.

6.10 In the safety set (all patients who received at least one application of study treatment and one post-baseline safety assessment), 38/53 (72%) of patients randomised to vPDT in RADIANCE, and [redacted] ([redacted]%) of patients randomised to vPDT in BRILLIANCE received at least one injection of ranibizumab subsequent to the allowance of treatment switching at Month 3. Therefore, only the results over the first 3 months of the study provide a reliable comparison of the clinical efficacy and safety of ranibizumab versus vPDT. The PSCR argued that allowing the vPDT arm of the trials to access ranibizumab at Month 3 was ethical and logical, reflecting the clinical value of ranibizumab in these patients.

6.11 The submission proposed a difference of at least 5 letters in the best corrected visual acuity (BCVA) as the minimal clinically important difference (MCID) between the ranibizumab groups and vPDT. It was claimed that this had been previously accepted by the PBAC to provide an effective improvement in vision-related quality of life. The PBAC previously considered that an increase of 5 letters or more might represent a clinically meaningful difference for some patients in the treatment of DME (Ranibizumab PSD, March 2013 PBAC Meeting). The PBAC clarified that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye will depend on the baseline VA of the patient in both eyes and on the subsequent overall VA during and after treatment. Those patients with well-preserved vision at baseline may experience a less clinically meaningful outcome than those patients with poorer vision at baseline (Ranibizumab-DME PSD, November 2013 PBAC Meeting). The PBAC subsequently recommended extending the listing of ranibizumab to include treatment of DME on the basis of treatment effects of this magnitude (Ranibizumab-DME PSD, July 2014 PBAC Meeting).

6.12 The key secondary outcome in both trials was to demonstrate non-inferiority of ranibizumab therapy guided by disease activity re-treatment criteria versus ranibizumab therapy guided by VA stabilisation criteria, as assessed by the difference between the average level of BCVA over all monthly post-baseline assessments (from Month 1 to Month 6) and the baseline level of BCVA. The pre-specified non-inferiority margin was 5 letters.

Comparative effectiveness

6.13 The results for the primary outcome in RADIANCE and BRILLIANCE, the difference between the average level of BCVA of the study eye from Month 1 through Month 3 and the baseline BCVA of the study eye, are summarised in Table 4.

Table 4: Average change in BCVA of the study eye from baseline to Month 1 through Month 3* (FAS, modified LOCF)

	Ranibizumab		vPDT
	Group I by VA stabilisation	Group II by disease activity	Group III
RADIANCE	**N=105[a]**	**N=116**	**N=55**
BCVA (letters), mean (SD)			
Baseline	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Average Month 1 to Month 3	66.0 (12.98)	66.4 (12.28)	56.9 (14.49)
Average change from baseline, mean (SD)	10.5 (8.16)	10.6 (7.26)	2.2 (9.47)
Comparison ranibizumab vs vPDT			
Difference in LS mean (95% CI)[b] p-value[c]	8.5 (5.8, 11.2) <0.00001	8.6 (6.1, 11.1) <0.00001	
BRILLIANCE	[redacted]	[redacted]	[redacted]
BCVA (letters), mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Average Month 1 to Month 3	[redacted]	[redacted]	[redacted]
Average change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Comparison ranibizumab vs vPDT			
Difference in LS mean (95% CI)[b] p-value[c]	[redacted]	[redacted]	

BCVA = best corrected visual acuity; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; vPDT = verteporfin photodynamic therapy.

[a] Of the 106 enrolled patients, 1 withdrew from the study before having a post-baseline VA assessment and was excluded from the analysis.

[b] Differences in LS means and the two-sided 95% CIs were estimated from pairwise ANOVA (stratified) model.

[c] One-sided p-values for the treatment difference were derived from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

* [redacted]

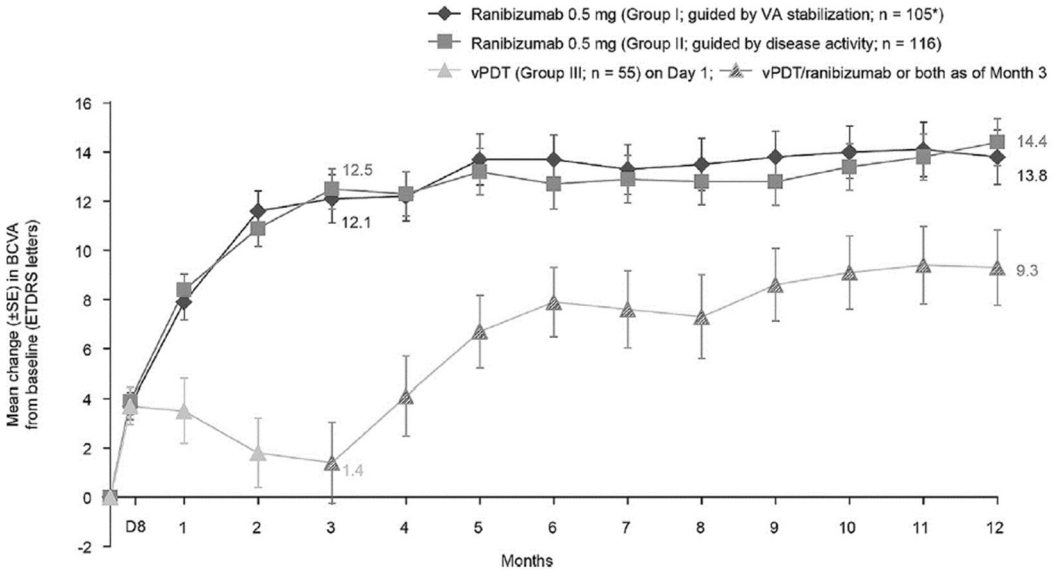
Source: Tables 2.5-1 and 2.5-2, p60 of the submission; Table 11-6 p133 RADIANCE CSR; Table 11-5 p85 BRILLIANCE CSR.

6.14 The submission claimed that in both RADIANCE and BRILLIANCE there was a statistically significant and clinically meaningful improvement in the average change in BCVA from baseline to Month 1 through Month 3 for both ranibizumab treatment groups compared with vPDT. This claim is reasonable if it is accepted that a difference of 5 letters is clinically important.

6.15 In both trials, the treatment effect in the subfoveal CNV subgroup was similar to that in the full analysis set (FAS). This finding supports the proposed PBS listing for the subfoveal CNV subgroup only.

6.16 The mean change from baseline in BCVA of the study eye over time in RADIANCE and BRILLIANCE is presented in Figures 1 and 2, respectively.

Figure 1: Mean change from baseline over time in BCVA of the study eye in RADIANCE (FAS, modified LOCF)



BCVA = best corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; SE = standard error; VA = visual acuity; vPDT = verteporfin photodynamic therapy

* Of the 106 enrolled patients, 1 withdrew from the study before having a post-baseline VA assessment and was excluded from the analysis.

Source: Figure 4, p687 Wolf et al (2014)[ii]

[ii] Wolf S, Balciuniene VJ*, et al.* RADIANCE: A randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014; 121 (3):682-92.

Figure 2: Mean change from baseline over time in BCVA of the study eye in BRILLIANCE (FAS, modified LOCF)

6.17 Ranibizumab treatment guided by either VA stabilisation or by disease activity led to a clinically meaningful improvement in BCVA at 3 months in both trials (approximately 10 letters), and the improvement in BCVA was maintained up to Month 12 in both ranibizumab treatment groups (Figures 1 and 2). An improvement in BCVA was also observed in the vPDT arm following the initiation of ranibizumab from Month 3 for patients randomised to receive vPDT. The treatment effect in the two ranibizumab arms was similar over the duration of the trial.

6.18 The results for key secondary outcome supported the claim that ranibizumab therapy guided by disease activity re-treatment criteria was non-inferior to ranibizumab therapy guided by VA stabilisation criteria, as assessed by the difference between the average level of BCVA over all monthly post-baseline assessments from Month 1 to Month 6 and the baseline level of BCVA, with a pre-specified non-inferiority margin of 5 letters (difference in least squares mean of 0.4 letters, 95% confidence interval: -1.3, 2.1).

6.19 Both RADIANCE and BRILLIANCE employed the National Eye Institute Visual Function questionnaire 25 (NEI-VFQ-25), which is used to measure vision-targeted health-related quality of life in patients with chronic eye conditions. The NEI-VFQ-25 consists of 25 items combined into 11 subscales. A 0-100 scale was used, with higher scores indicating better functioning. The results for the composite score are presented in Table 5.

Table 5: Change in NEI VFQ-25 composite score from baseline to Month 3 (FAS, LOCF)

	Ranibizumab		vPDT
	Group I by VA stabilisation	Group II by disease activity	Group III
RADIANCE	**N=105**	**N=116**	**N=55**
Baseline, mean (SD)	69.3 (17.86)	71.0 (17.77)	71.9 (17.42)
Month 3, mean (SD)	74.6 (16.81)	75.2 (17.24)	72.2 (18.37)
Change from baseline, mean (SD)	5.3 (13.96)	4.3 (10.09)	0.3 (12.63)
Comparison with vPDT			
Difference in means (95% CI)	5.0 (0.1, 10.0)	3.9 (0.0, 7.9)	
BRILLIANCE	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Month 3, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Comparison with vPDT			
Difference in means (95% CI)	[redacted]	[redacted]	

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; NEI VFQ = national Eye Institute Visual Function questionnaire; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy
Source: Tables 2.5-13 and 2.5-14, p70 of the submission.

6.20 The submission stated that, in both RADIANCE and BRILLIANCE, mean changes in scores at Month 3 tended to be in favour of ranibizumab compared to vPDT for most scores (composite score, general vision, near activities, distance activities, mental health, role difficulties, dependency and peripheral vision scores). In the two ranibizumab treatment arms, the changes from baseline in these subscales scores and in the composite score were maintained at Months 6 and 12. The clinical importance of the observed improvements in scores was not addressed in the submission. As for the other outcomes, comparative data were only available to Month 3 of the trial.

Comparative harms

6.21 Table 6 summarises the treatment exposure to both ranibizumab and vPDT in each treatment arm in RADIANCE and BRILLIANCE.

Table 6: Ranibizumab and vPDT treatment exposure from Day 1 to Month 12 (Safety set)

	Ranibizumab				vPDT	
	Group I by VA stabilisation		Group II by disease activity		Group III	
	RADIANCE	**BRILLIANCE**	**RADIANCE**	**BRILLIANCE**	**RADIANCE**	**BRILLIANCE**
RANIBIZUMAB	N=106	[redacted]	N=118	[redacted]	N=38[a]	[redacted][a]
Injections per patient						
Mean (SD)	4.6 (2.59)	[redacted]	3.5 (2.92)	[redacted]	3.2 (2.54)	[redacted]
Median (range)	4.0 [redacted]	[redacted]	2.5 [redacted]	[redacted]	2.0 [redacted]	[redacted]
vPDT	NA	NA	NA	NA	N=53	[redacted]
Treatments per patient						
Mean (SD)					1.04 (0.19)[b]	[redacted][b]
Median (range)					1 [redacted][c]	[redacted][d]

SD = standard deviation; vPDT = verteporfin photodynamic therapy; NA = not applicable.
[a] Patients randomised to vPDT who received at least 1 dose of ranibizumab as of Month 3.
[b] Calculated during the evaluation.
[c] 2 patients in Group III who did not receive any ranibizumab after Month 3 received a second treatment with vPDT (1 at Month 3, and 1 at

Month 5) (Section 2.1.3, p160 RADIANCE CSR).

[d] 3 patients in Group III who received ranibizumab after Month 3 also received a second dose of vPDT (1 at Month 6, 1 at Month 7 and 1 at Month 11) (Table 14.3-1.4.2 p975 BRILLIANCE CSR)

Source: Tables 2.5-11 and 2.5-12, pp68-9 of the submission; Section 12.1.2-12.1.3 RADIANCE CSR; Table 14.3-1.4.2 p 975 BRILLIANCE CSR)

6.22 In both trials, the mean number of ranibizumab injections per patient was higher in the ranibizumab arm with retreatment guided by VA stabilisation (Group I) compared with the ranibizumab arm with retreatment guided by disease stabilisation (Group II).

6.23 The submission presented 12-month safety results for the subgroups of patients in the vPDT treatment arm who did (n=38) and did not (n=15) receive ranibizumab after Month 3. The subgroup of patients in the vPDT arm who did not receive ranibizumab subsequent to Month 3 was not a randomised group; these patients were likely to differ from those in the complementary subgroup who did receive ranibizumab in terms of both baseline prognostic factors and response to therapy.

6.24 Of the patients in the vPDT arms of the trials who did not receive ranibizumab, only 2/15 (13.3%) in RADIANCE and [redacted] in BRILLIANCE received a second vPDT treatment over the 12 months of the trial[iii]. The remaining patients did not receive any further study treatment. Consequently, there were no data regarding adverse events (AEs) associated with repeated exposure to vPDT. The ESC considered that the lack of continuing treatment with vPDT in the trials highlighted the lack of clinical effectiveness of this alternative therapy.

6.25 A summary of the key AEs over the 12-month study period of the trials is presented in Table 7.

[iii] Source: Table 14.3-1.4.2 of the RADIANCE and BRILLIANCE Clinical Study Reports.

Table 7: Summary of key adverse events in the randomised trials up to Month 12*

Trial ID	Ranibizumab		vPDT	
	Group I by VA stabilisation n (%)	Group II by disease activity n (%)	Group III With ranibizumab from Month 3 n (%)	Group III without ranibizumab from Month 3 n (%)
RADIANCE	**N=106**	**N=118**	**N=38**	**N=15[b]**
Mean duration of follow-up, days (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE				
Ocular AEs	46 (43.4)	44 (37.3)	16 (42.1)	4 (26.1)
Non-ocular AEs	48 (45.3)	51 (43.2)	19 (50.0)	5 (33.3)
Serious AEs	7 (6.6)	6 (5.1)	0	0
Non-ocular AEs	6 (5.7)[a]	5 (4.2)	0	0
Study eye	1 (0.9)	1 (0.8)	0	0
Discontinued due to AEs	0	0	0	0
BRILLIANCE	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of follow-up, days (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Any AE				
Ocular AEs	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular AEs	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular AEs	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]
Fellow eye	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to AE	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to SAE	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; n = number of participants reporting data; N = total participants in group; SAE = serious adverse event; VA = visual acuity; vPDT = verteporfin photodynamic therapy

[a] There were a total of 7 serious AEs, as two AEs were reported for one patient.

[b] Only 2/15 patients received any additional vPDT treatments beyond the initial treatment at Day 1

[c] None of these patients received any additional vPDT treatments beyond the initial treatment at Day 1

* Mean number of treatments to Month 12 (safety set): RADIANCE Group I = 4.6 injections ranibizumab, Group II = 3.5 injections ranibizumab, Group III = 1.0 vPDT treatment; Group III with ranibizumab (n=38) = 3.2 injections ranibizumab [redacted]

Source: Tables 2.5-16 and 2.5-17, pp72-3 of the submission.

6.26 The submission stated that, in both trials, the frequency of ocular and non-ocular AEs was comparable across the three treatment groups, with the patients without ranibizumab treatment in Group III experiencing a numerically smaller frequency of AEs. The majority of patients in Group III had received ranibizumab. While no serious AEs were reported in patients in the vPDT treatment arms who did not receive ranibizumab, as discussed above, the use of vPDT in these subgroups was unlikely to reflect the use of vPDT in clinical practice where ranibizumab is currently not PBS-subsidised for the treatment of CNV due to PM.

6.27 The most frequent ocular AE in patients receiving ranibizumab was conjunctival haemorrhage, which occurred in approximately 11% and [redacted]% of patients in the ranibizumab arms (combined Groups I and II) in RADIANCE and BRILLIANCE,

respectively, over the 12 months of the trial. The submission noted that this AE is extremely common in clinical practice, is not a serious complication and that, with rare exceptions, the haemorrhage resolves spontaneously within 2 weeks without treatment.

6.28 The TGA delegate concluded that the AE profile of ranibizumab 0.5 mg for the proposed use in CNV due to PM was consistent with the known profile of ranibizumab in previously approved indications. The ocular safety concerns identified in the risk management plan (RMP) include [redacted] Systemic safety concerns include [redacted]

Benefits/harms

6.29 A summary of the comparative benefits for ranibizumab over vPDT is presented in the table below. There were insufficient comparative safety data to allow a reliable comparison of harms.

Table 8: Summary of comparative benefits and harms for ranibizumab and vPDT

Benefits							
Average change in best corrected visual acuity (BCVA) of the study eye from baseline to Month 1 through Month 3							
Trial	**Ranibizumab**			**vPDT**			**Mean difference*: Ranibizumab vs. vPDT[a] (95% CI)**
	N	**Mean Δ baseline (letters)**	**SD**	**N**	**Mean Δ baseline (letters)**	**SD**	
Ranibizumab by VA stabilisation (Group I) vs vPDT							
RADIANCE	105	10.5	8.16	55	2.2	9.47	8.5 (5.8, 11.2)
BRILLIANCE	[redacted]						
Ranibizumab by disease activity (Group II) vs vPDT							
RADIANCE	116	10.6	7.26	55	2.2	9.47	8.6 (6.1, 11.1)
BRILLIANCE	[redacted]						

AE = adverse events; RD = risk difference; RR = risk ratio; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy

* [redacted]

[a] Difference in LS means estimated from pairwise ANOVA (stratified) model.

Source: Tables 2.5-1 and 2.5-2, p60 of the submission; Table 12-1 p155 and Table 12-5 p159 RADIANCE CSR; Table 12-1 p100 and Table 12-4 p103 BRILLIANCE CSR.

6.30 On the basis of the direct evidence presented by the submission, the comparison of ranibizumab and vPDT resulted in approximately a 5 to 9 letter improvement in mean average change in best corrected visual acuity of the study eye from baseline to Month 1 through Month 3. The PBAC previously considered that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye will depend on the baseline visual acuity of the patient in both eyes and on the subsequent overall visual acuity during and after treatment. Those with well-preserved vision at baseline may experience a less clinically meaningful outcome

than those patients with poorer vision at baseline (Ranibizumab-DME PSD, November 2013 PBAC Meeting). The mean BCVA at baseline was 55 letters in the RADIANCE trial and [redacted] in the BRILLIANCE trial, with having greater than 70 letters across both eyes being the legal requirement to hold a driver's licence.

Clinical claim

6.31 The submission described ranibizumab as superior in terms of effectiveness and non-inferior in terms of safety compared to vPDT.

6.32 The evidence presented in the submission supported the conclusion that ranibizumab is statistically superior to vPDT in terms of the mean average improvement in BCVA of the study eye from baseline to Month 1 through Month 3. The PBAC considered that the claim of superior efficacy over vPDT was reasonable.

6.33 There were no randomised comparative effectiveness data beyond 3 months, and the submission did not present any data on the long-term effectiveness of ranibizumab beyond the 12-month duration of the trials. The Pre-Sub-Committee response (PSCR) highlighted the observational study by Tan et al 2017,[iv] which reported ranibizumab outcomes in the east-Asian cohort of the RADIANCE trial to 48 months (n=16), supported the long-term safety and efficacy of ranibizumab. The PBAC considered that data from Tan et al 2017 provided some support of the long-term safety and efficacy of ranibizumab.

6.34 The safety profile of ranibizumab in patients with CNV due to PM was consistent with that observed in other indications. As randomised comparative safety data were only available over the first 3 months of the study, the comparative safety of ranibizumab versus vPDT for the treatment of CNV due to PM beyond 3 months could not be reliably determined. The ESC noted that there were no new safety signals with use of ranibizumab in CNV due to PM. Although insufficient data were available to adequately evaluate the safety of ranibizumab compared with vPDT, the PBAC considered that, based on the available data and supporting data from Tan et al 2017, it was reasonable to accept that the safety profile of ranibizumab in this indication is consistent with its safety profile for its other indications.

6.35 This clinical claim against vPDT is not directly informative to the assessment of cost-effectiveness if vPDT is not the appropriate comparator for ranibizumab in this population. The PBAC considered that the claim of superior efficacy over vPDT could be reasonably extended to include superior efficacy over sham injection (no treatment).

[iv] *Tan NW, Ohno-Matsui K, Koh HJ, Nagai Y, Pedros M, Freitas RL, et al. 'Long-term outcomes of ranibizumab treatment of myopic choroidal neovascularization in east-Asian patients from the RADIANCE study'. Retina (Philadelphia, Pa). 2017*.

Economic analysis

6.36 The submission presented a stepped economic evaluation based on a direct randomised trial (RADIANCE) and implementing a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis. The model structure and rationale are summarised below.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	A 10 year time horizon was presented in the base case. This is compared with 12 months in the trial, with comparative efficacy data being available for only 3 months. A 5 year time horizon and a lifetime horizon are tested in sensitivity analyses.
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	[redacted]
Cycle length	1 month
Transition probabilities	Transition probabilities for the first year were sourced from the key trial (RADIANCE); transition probabilities for the subsequent years were assumed to be constant over the entire model time horizon. The long term transition probabilities were extrapolated based on within trial data, assuming the rate of worsening being the average of worsening rate in Month 3-12 of the trial; and the rate of improving being 50% of the average of improvement rate in Month 3-12 of the trial.

LYG = life years gained; QALY = quality-adjusted life years; ETDRS = Early Treatment Diabetic Retinopathy Study; VA = visual acuity.
Source: Table 3.1-1, p81 of the Submission.

6.37 This economic evaluation was not informative to the PBAC given that:

- vPDT is not the appropriate comparator for ranibizumab in this population; and
- the PBAC has previously considered that vPDT was not cost-effective for this population, with an incremental cost effectiveness ratio (ICER) of more than $200,000/QALY compared with placebo (Section 12, Verteporfin PSD, November 2015 PBAC Meeting).

6.38 The economic model used evidence from Group II (ranibizumab arm, re-treatment determined by disease activity) and a subgroup of Group III (vPDT arm) of the RADIANCE trial to model the efficacy of treatment. Using results from RADIANCE may be reasonable given that a multicultural population was included in the trial, although analysis of RADIANCE trial data did not indicate evidence of treatment effect modification by race (Caucasian vs Asian). In addition, the BRILLIANCE trial showed a [redacted] comparative benefit for ranibizumab relative to vPDT. In both ranibizumab trials, the mean number of ranibizumab injections per patient was higher when retreatment was guided by VA stabilisation (Group I; 4.6 injections for both RADIANCE and BRILLIANCE) compared with retreatment being guided by disease stabilisation (Group II; RADIANCE 3.5 injections; BRILLIANCE [redacted]). If clinicians use a mixture of these two methods in clinical practice, the number of injections of ranibizumab may have been underestimated in the model. Nonetheless, the modelled health outcomes are not particularly sensitive to this variable, although

the incremental costs would increase substantially with longer duration of ranibizumab therapy. By relying on the RADIANCE trial only, with its numerically larger incremental effectiveness and numerically fewer subsequent injections, a more favourable ICER was generated than if the model had relied on a synthesis of the two trials. The ESC considered that the submission did not provide a strong justification for not also relying on the BRILLIANCE trial for its modelling, however the ESC also advised that a number of sensitivity analyses varying the frequency of injections and duration of therapy showed the ICER was more sensitive to the assumed number of ranibizumab injections per patient (see Table 14).

6.39 The submission considered the following scenarios:

- Patients receiving treatment in the better seeing eye (BSE)
- Patients receiving treatment in the worse seeing eye (WSE)
    - where the treated eye remains the WSE
    - where the treated eye becomes the BSE
- Patients receiving treatment in both eyes

The model presented ICERs for each scenario as well as a weighted ICER.

6.40 The model did not include the cost or quality of life impact of treatment-related adverse events. This may not be reasonable. However, there were very limited comparative safety data available from the trial.

6.41 The transition probabilities between the VA health states are highly uncertain. In the first year, the transition probabilities between health states were as observed from 116 patients in the ranibizumab arm (Group II) and 15 patients in the vPDT arm of RADIANCE. For patients receiving vPDT, transition probabilities were only based on 15 patients who did not switch to ranibizumab treatment in the first 12 months. The vast majority of these 15 patients did not actually receive any further treatment (only 2/15 received a second treatment with vPDT). Nearly all patients in the vPDT arm who met the re-treatment criteria received ranibizumab. Therefore, these 15 patients are likely to only represent the subgroup of patients who did not meet the re-treatment criteria. In contrast, [redacted] patients in the ranibizumab arm met the re-treatment criteria and received further treatment. Transition probabilities for ranibizumab and for vPDT were likely derived from two incomparable populations from the RADIANCE trial. Additionally, as these transition probabilities were derived from a small number of patients they were unlikely to be reliable. Alternative approaches may be used to calculate transition probabilities in the comparator arm based on the vPDT ITT population (as recommended for the base case in the PBAC Guidelines) or an adjustment for switching using appropriate methods such as the Rank Preserving Structural Failure Time (RPSFT) model, or the Inverse Probability of Censoring Weights (IPCW).

6.42 The PSCR suggested that randomisation-based adjustment methods and observational-based methods such RPSFT model or the IPCW and structural nested models (SNM) are particularly sensitive to bias when the switching proportion is very

high and the RCT dataset is of relative small size. The ESC noted that this response did not address the recommended use of the vPDT ITT population, and advised that the biases involved with censoring out patients as adopted for the model had been shown through simulation modelling[v] to be associated with greater biases than the statistical adjustment methods dismissed by the sponsor.

6.43 The submission assumed constant transition probabilities beyond Month 12 for the entire model time horizon. These long-term transition probabilities for both arms were estimated using the short term probabilities observed from RADIANCE under two main assumptions:

- the rate of worsening beyond Month 12, is calculated as being the average of worsening rate in Month 3-12 of the trial; and
- the rate of improving beyond Month 12, is calculated as being 50% of the average of the improvement rate in months 3-12 of the trial.

6.44 Long-term outcomes of ranibizumab treatment of myopic CNV in east-Asian patients from the RADIANCE trial have been available for up to 48 months (Tan et al, 2017, provided with the submission). It is unclear whether the long term data for the ITT population of RADIANCE are available. Long term data from RADIANCE were not used in the model. The PSCR defended the approach to modelling long-term transition probabilities based on assumptions (using clinical advice and long-term data in east-Asian patients from RADIANCE reported in Tan et al (2017)) that the rate of improvement from 2 years onwards would reduce over time and the rate of worsening would stay constant, with a net decline in vision. The ESC noted that that the PSCR also reported improvements in visual acuity from Tan et al (2017) of +10.4 ±22.3 letters at 24 months and +16.3 ±18.7 letters at 48 months, which provided some support to assume that a net decline in vision was a conservative approach in the modelling.

6.45 The number of treatments for both ranibizumab and vPDT is uncertain given the lack of long term data.

6.46 The model included the cost of falls that was associated with the VA3 and VA4 health states and the cost of blindness that was associated with VA4 health state. These costs are consistent with those used in the previous ranibizumab submissions for both DME and retinal vein occlusion (RVO). The PBAC previously considered that, as the costs of blindness included any medical expenditure associated with blindness, it was likely that this approach also included the cost of falls. The ESC advised that including the costs of both falls and blindness would be double counting and the costs of falls should be removed from the economic evaluation. Since the model

[v] Latimer N et al. Assessing methods for dealing with treatment crossover in clinical trials: a follow-up simulation study. Discussion paper 14.01, School of Health and Related Research, The University of Sheffield. 5 March 2014.

estimated more blindness in the vPDT arm than in the ranibizumab arm, the cost of blindness contributed substantially to the cost-offsets and may have underestimated the incremental cost of ranibizumab compared with vPDT.

6.47 The key drivers of the model are summarised below.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Comparator	vPDT	High, favours ranibizumab
Extrapolation	Based on a small subgroup of the trial for the vPDT arm	Uncertain
Cost of blindness	Cost of blindness associated with VA4 in addition to cost of falls	Moderate, favours ranibizumab

vPDT = verteporfin photodynamic therapy.
Source: compiled during the evaluation based on Sections 3.4, 3.6 and 3.9 of the submission.

6.48 The results of stepped economic evaluation are presented in the table below.

Table 11: Presentation of the stepped economic evaluation (weighted for treatment scenarios of bilateral treatment, treatment in BSE and WSE)

	Ranibizumab	vPDT	Incremental
Step 1 – trial based analysis			
Cost	$[redacted]	$[redacted]	-$[redacted]
Mean change in BCVA at Month 12*	[redacted]	[redacted]	[redacted]
Cost per additional letter gained			[redacted]
Step 2 – Cost utility analysis at Month 12 including drug cost only			
Cost	$[redacted]	$[redacted]	-$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Cost per QALY gained			[redacted]
Step 3 – Cost utility analysis at Year 10 including administration and monitoring costs			
Cost	$[redacted]	$[redacted]	-$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Cost per QALY gained			[redacted]
Step 4 – Cost utility analysis at Year 10 including all costs			
Cost	$[redacted]	$[redacted]	-$[redacted]
Revised^	$[redacted]	$[redacted]	-$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Cost per QALY gained			[redacted]

*Results for Group II and vPDT treatment arms from RADIANCE
^ This table in the submission was inconsistent with the results provided in other tables, and the results provided in EconomicModel_Ranibizumab_PM.xlsx, Results sheet.
vPDT = verteporfin photodynamic therapy; BCVA = best corrected visual acuity; QALY = quality-adjusted life year.
Source: Table 3.8-2, p 109, Section 3 of the submission

6.49 The results of the economic evaluation indicated that ranibizumab dominated vPDT for the treatment of CNV secondary to PM. This is primarily due to the higher cost and lower effect of vPDT than ranibizumab. The PBAC had previously considered that vPDT is not cost-effective compared with placebo in the treatment of CNV secondary to PM.

6.50 The submission has conducted a range of sensitivity analyses, but none of them could address the concern regarding the inappropriateness of the comparator.

Additional analyses for PBAC consideration

6.51 The appropriateness of the comparator (vPDT) was noted as a major concern, given the lack of cost-effectiveness of vPDT (large cost and small effect). In its consideration of verteporfin for PM in November 2005, the PBAC noted that the statistically significant reduction in risk of visual loss at 12 months did not persist at 24 months. Thus, it is not clear that there is a worthwhile verteporfin treatment effect in this population. Small modelled incremental benefits for this population resulted in a highly uncertain and unacceptably high cost-effectiveness ratio (Section 10, Verteporfin PSD, November 2005 Meeting).

6.52 If PBAC accepts other parameters in the economic model as reasonable, a pragmatic (and possibly conservative) approach would be to model the cost-effectiveness of ranibizumab versus sham injection, by removing the cost associated with vPDT and its administration, while assuming the same treatment effect and healthcare resource consequences as originally modelled for the vPDT arm (see analysis #1 in Table 12 below). It is noted that this is likely to overestimate the health outcomes associated with sham for this indication if the PBAC accepts the submission's approach to modelling the vPDT arm, but may be informative to the PBAC. It was acknowledged that the effect of vPDT estimated in the model is highly uncertain, given that they were derived from only 15 patients and 13 of them were not eligible for re-treatment (guided by disease activity) as observed in RADIANCE. Thus if the PBAC accepted this general approach, but would prefer the transition probabilities to be driven by the ITT population of the vPDT arm, this analysis could have been provided by the submission.

6.53 The PSCR provided a revised ICER using the sham arm of the VIP trial[vi] which compared vPDT and sham. This revised ICER maintained the dominance of ranibizumab over sham. However, the ESC was unable to verify the indirect comparison between the RADIANCE and VIP trials and the revised ICER. Nonetheless, even under the conservative assumptions of no vPDT costs and no risk of falls using the modelled RADIANCE trial data, the ICER remained less than $15,000 per QALY gained. This was, however, still sensitive to the frequency of injections and duration of therapy with ranibizumab (see Table 14).

6.54 In the consideration of ranibizumab for both DME and RVO, the Commentary, ESC and PBAC each provided a different revised base case. A summary of differences in key variables between the current submission, and the revised base case estimates for the ranibizumab submissions for DME and RVO (July 2014 PBAC meeting) are provided in Table 12.

[vi] *Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1. Ophthalmology. 2001;108(5):841-52.*

Table 12: Differences in key variables: Current submission vs respecified base cases in the Commentary, ESC advice and PBAC minutes for ranibizumab for DME and RVO (July 2014 PBAC Meeting)

Base case	Variables			
	Utilities	Cost of blindness	Risk/cost of falls	Mortality
Current submission	AQoL-7D: econometric transformation	Clarke 2008	Risk: BMES Cost: Watson et al, 2011 inflated to current prices	Christ 2008 (RR=1.13)
July 2014 ranibizumab submissions: Commentary	AQoL-7D: econometric transformation	Clarke 2008	Risk: BMES Cost: Mathers and Penn 1999 inflated to current prices	BMES (RR=1.32)
July 2014 ranibizumab submissions: ESC Advice	AQoL-7D: econometric transformation	Not included	Not included	Christ 2008 (RR=1.13)
July 2014 ranibizumab submissions: PBAC minutes	AQoL-7D: econometric transformation	Clarke 2008	Not included	Christ 2008 (RR=1.13)

RR = relative risk; BMES = Blue Mountains Eye Study.
Source: Compiled during the evaluation

6.55 The additional sensitivity analyses in Table 13 were provided for the PBAC's consideration, aligned with variables suggested by the previous Commentary, ESC Advice and PBAC minutes as described in the table above. The ICER ranged from less than $15,000/QALY when removing the costs associated with the administration of vPDT, to less than $15,000/QALY using the variables from the July 2014 PBAC minutes and $15,000/QALY - $45,000/QALY using the variables in the July 2014 ESC Advice for the ranibizumab submissions. When removing the costs associated with blindness, costs of falls, monitoring costs and increased risk of mortality, the ICER increased to$45,000/QALY - $75,000/QALY. These sensitivity analyses show that the model is most sensitive to the exclusion of cost offsets associated with blindness. The ESC considered that the costs associated with blindness were appropriate, but that also including the cost of falls represented double counting. The ICER with the removal of the cost of vPDT and the risk of falls was calculated to be less than $15,000/QALY gained.

Table 13: Results of additional univariate and multivariate sensitivity analyses conducted during the evaluation

#	Aspect	Base case value	Tested value or range		Rani	vPDT	Incremental
	Base case (as per submission)	Costs			$ [redacted]	$ [redacted]	-$ [redacted]
		QALYs			[redacted]	[redacted]	[redacted]
		Cost per QALY					[redacted]
	Sensitivity analyses						
#	**Aspect**	**Base case value**	**Tested value or range**		**Rani**	**Sham**	**Incremental**
1	Cost associated with vPDT	Assume 3.4 administrations in year 1, and 1.7 administrations in year 2.	Assume no administrations of vPDT (and holding efficacy constant)	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY			$ [redacted]
2	#1 AND relative risk of falls (consistent with PBAC base case in July 2014 ranibizumab submissions)	As per #1 above, and RR VA1 = 1 RR VA2 = 1 RR VA3 BSE = 1.55 RR VA3 WSE = 1 RR VA4 BSE = 1.55 RR VA4 WSE = 1	As per #1 above, and RR = 1	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	0.17
				Cost per QALY			$ [redacted]
3	#1 and cost associated with blindness	As per #1 above, and Year 1 - $ [redacted] per month Subsequent years - $ [redacted] per month	As per #1 above, and $0.00	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY			$ [redacted]
4	#1 and #2 and #3 (consistent with ESC base case in July 2014 PBAC submissions)	As per #1, #2 and #3 above	As per #1, #2 and #3 above	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY			$ [redacted]
5	#1 and number of visits for monitoring	As per #1 above, and Year 1: 8 Year 2: 4 Year 3: 1 Year 4: 1 Year 5: 1	As per #1 above, and Number of visits over time horizon of the model: 0	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY			$ [redacted]
6	All of the above	As per #1, #2, #3, and #5	As per #1, #2, #3, and #5	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY			$ [redacted]

Rani = ranibizumab; QALY = quality adjusted life years; RR = relative risk; vPDT = verteporfin photo dynamic therapy; BSE = better-seeing eye; WSE = worse-seeing eye.
Source: compiled during the evaluation, based on EconomicModel_ranibizumab_PM.xlsx as provided by the submission.

The redacted table shows ICERs in the range of less than $15,000/QALY to $75,000/QALY.

6.56 The ESC also considered there was considerable uncertainty in the frequency and duration of injections of ranibizumab, with the number of injections varying between trials and whether treatment was guided by visual acuity stabilisation or by disease

activity (see Table 6). The ESC noted that the PBAC recommendation for ranibizumab in AMD was based on a monthly dosing schedule and up to 15 injections per patient. The June 2015 DUSC utilisation review of AMD[vii] revealed that experience with ranibizumab in treating AMD showed in clinical practice the number of injections may be greater than anticipated. The review found from 2011 onwards the number of injections per patient appeared to have stabilised, with new patients receiving an average of 8.4 injections in their first year of treatment, and continuing patients receiving an average of 7.1 injections per year. The majority of patients remained on treatment for many years. Approximately half of patients are treated for at least 4 years, with 40% of patients still treated 6-7 years after initiation. Therefore, the ESC provided a number of further sensitivity analyses to test how much changing the frequency and duration was driving the overall cost-effectiveness (see Table 14 below). It should be noted that only the impact on costs has been assessed in the sensitivity analyses presented in Table 14.

[vii] http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/aflibercept-ranibizumab-prd-2015-06

Table 14: Results of additional univariate and multivariate sensitivity analyses provided by the ESC

#	Aspect	Base case value	Tested value or range		Rani	vPDT	Incremental
	Base case (as per submission)	Costs			$ [redacted]	$ [redacted]	-$ [redacted]
		QALYs			[redacted]	[redacted]	[redacted]
		Cost per QALY			[redacted]	[redacted]	[redacted]
Exploratory analyses							
#	**Aspect**	**Base case value**	**Tested value or range**		**Rani**	**No active treatment**	**Incremental**
1	Cost associated with vPDT	Assume 3.4 administrations in year 1, and 1.7 administrations in year 2.	Assume no administrations of vPDT (and holding efficacy constant)	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
2	#1 AND relative risk of falls (consistent with PBAC base case in July 2014 ranibizumab submissions)	As per #1 above, and RR VA1 = 1 RR VA2 = 1 RR VA3 BSE = 1.55 RR VA3 WSE = 1 RR VA4 BSE = 1.55 RR VA4 WSE = 1	As per #1 above, and RR = 1	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
3	#1 AND number of ranibizumab administrations	As per #1 above and assume 3.5 administrations in year 1 and 1 administration in year 2.	Assume 3.5 administrations in all years	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
4	#1 AND #2 AND #3	See above.	See above.	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
5	#1 AND number of ranibizumab administrations	As per #1 above and assume 8.4 administrations in year 1 and 7.1 administrations in year 2	Assume 8.4 administrations in year 1 and 7.1 administrations in year 2	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
6	#1 AND #2 AND #5	See above.	See above.	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
7	#1 AND number of ranibizumab administrations	As per #1 above and assume 8.4 administrations in year 1 and 7.1 administrations in year 2	Assume 8.4 administrations in year 1 and 7.1 administrations in all subsequent years	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]
8	#1 AND #2 AND #7	See above.	See above.	Costs	$ [redacted]	$ [redacted]	$ [redacted]
				QALYs	[redacted]	[redacted]	[redacted]
				Cost per QALY	[redacted]	[redacted]	$ [redacted]

Rani = ranibizumab; QALY = quality adjusted life years; RR = relative risk; vPDT = verteporfin photo dynamic therapy; BSE = better-seeing eye; WSE = worse-seeing eye.

Source: compiled during the evaluation, based on EconomicModel_ranibizumab_PM.xlsx as provided by the submission.

The redacted table shows ICERs in the range of less than $15,000/QALY to more than $200,000/QALY.

6.57 The pre-PBAC Response argued that the sensitivity analyses provided by the ESC were conservative as they assumed no treatment effect beyond Year 1 and clinicians would be unlikely to continue treatment with ranibizumab in the absence of a treatment effect. The pre-PBAC Response provided additional sensitivity analyses applying the number of injections for the treatment of CNV secondary to PM sourced from a literature search where the ICER ranged from [redacted] to less than $15,000 per QALY gained. The PBAC noted that the data used to inform these alternative sensitivity analyses had not been evaluated.

Drug cost/patient/year: $[redacted]

6.58 The cost/patient/year was estimated to be $[redacted]. This was calculated assuming an average of 3.5 treatments per patient for unilateral treatment, as was observed over the 12 months following randomisation for Group II in the RADIANCE trial, and a cost per treatment of $[redacted].

Estimated PBS usage & financial implications

6.59 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the use and financial impact of listing ranibizumab for the treatment of subfoveal CNV due to PM.

6.60 The prevalence of PM in the Australian population aged ≥40 years was assumed to be 1.18%. The submission stated that this was the average of Australian/European/US prevalence rates reported in the published literature. This was a major source of uncertainty in the financial estimates. The reported prevalence rates used in the submission's estimate ranged from 0.05% to 4.0% and were based on populations varying in both age range and ethnicity.

6.61 The incidence of CNV in patients with PM was sourced from Ohno-Matsui et al (2003). Ohno-Matsui et al (2003) was a retrospective study using clinical records from 218 consecutive patients (325 eyes). As eyes/patients with a follow up of less than 3 years were excluded from the study, there was considerable risk of selection bias. The number excluded on this basis was not reported. The potential effect of this bias on the estimated probability of patients with PM developing CNV was uncertain.

6.62 The average number of ranibizumab injections per patient was consistent with that used in the cost-effectiveness analysis, but also incorporated the assumption that [redacted]% of incident patients require bilateral treatment (increasing the number of injections from 4.5 in the economic analysis to 5.5 in the financial estimates). Patients were assumed to receive all treatment in their incident year; patients receiving treatment beyond 12 months were not carried forward to the following year as prevalent cases.

6.63 The submission assumed that PBS-subsidised verteporfin, ranibizumab and aflibercept are currently being accessed for the treatment of CNV due to PM outside the PBS restriction for CNV due to AMD. The submission offset the estimated costs associated with this use of ranibizumab, aflibercept and verteporfin outside of their current restrictions, on the basis that this would no longer occur once a legitimate PBS option was available. No substantive evidence to support the frequency of use outside the current restrictions was provided in the submission. There was insufficient information provided in the submission to determine whether the clinicians informing the assumption are representative of current prescribers or have knowledge of prescribing patterns. Importantly, it would be difficult for a sample of clinicians to be able to accurately report on the extent of prescribing outside the PBS restrictions in clinical practice. This could only be accurately achieved through a formal audit of all RPBS/PBS claims. The PSCR did not agree that it was inappropriate to include cost offsets for existing treatments and argued that it is very unlikely that the condition would be left untreated on the basis that it is highly symptomatic and affects a relatively young population. The ESC considered that in the absence of any data that reports on the extent of prescribing with relative accuracy, it would not be appropriate to include cost offsets for prescribing of PBS listed medicines outside their PBS restrictions.

6.64 The estimated use and financial implications to the PBS/RPBS and the MBS of listing ranibizumab for the treatment of CNV secondary to PM are summarised in Table 15.

Table 15: Estimated use and financial implications (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of ranibizumab for CNV secondary to PM						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ranibizumab for CNV secondary to PM						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for current use of ranibizumab, aflibercept and verteporfin						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications to the Australian government health budget						
Net cost to PBS/RPBS *Cost without offsets due to use of PBS-listed drugs outside the PBS restriction.*	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS *Cost without offsets due to use of PBS-listed drugs outside the PBS restriction.*	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]

[a] Assuming 5.5 scripts per year as estimated by the submission.

Figures in italics were calculated during the evaluation, excluding cost offsets associated with use of PBS-listed medicines outside the PBS restriction for CNV due to AMD.
Source: Table 4.2-2 p122, Table 4.5-4, p137 and Table 4.5-6, p138 of the submission.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000 per year, and the net cost to the PBS would be less than $10 million per year.

6.65 The main source of uncertainty in the financial estimates was the size of the eligible patient population. The estimated net cost to the PBS/RPBS could be either over- or under-estimated. The ESC also considered that the financial implications would be sensitive to the number of injections per patient, but was unsure whether the sponsor's offer in relation to the Risk Sharing Arrangements might address this source of uncertainty.

Financial Management – Risk Sharing Arrangements

6.66 The sponsor proposed that ranibizumab usage in CNV due to PM should be listed at the same published and effective price as the AMD indication and should be incorporated into the RSA negotiated to cover that indication.

6.67 The proposal in the submission, which was restated in the PSCR, was to have the requested indication in CNV due to PM included in the existing Deed of Agreement for ranibizumab used in AMD, to mitigate the risk to the Australian Government of inaccuracies in the estimates. The submission stated that further discussion between the sponsor and the Department of Health would be required for a number of logistical arrangements including:

- future capping arrangements
- possible means of identifying CNV secondary to PM usage separate of AMD and RVO usage (such as separate PBS item numbers for each indication)
- ways in which ranibizumab usage in CNV secondary to PM can be differentiated from aflibercept usage which currently shares the same expenditure cap.

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

7 PBAC outcome

7.1 The PBAC recommended extending the listing of ranibizumab as an Authority required benefit to include treatment of subfoveal choroidal neovascularisation (CNV) secondary to pathologic myopia (PM). The PBAC was satisfied that ranibizumab provides, for some patients, a significant improvement in efficacy compared with no treatment. The PBAC's recommendation for listing was primarily based on its assessment that the cost-effectiveness of ranibizumab would be acceptable at the price proposed in the submission across a wide range of scenario and sensitivity analyses.

7.2 The PBAC considered there was a clinical need for PBS subsidised treatments for CNV secondary to PM noting that there are currently no PBS listed therapies for the

treatment of this condition.

7.3 The PBAC considered that, consistent with existing administrative arrangements for ranibizumab and aflibercept in subfoveal CNV due to age-related macular degeneration (AMD), authority applications would be appropriate. The PBAC advised that the current PBS listing for CNV due to AMD could be amended to allow for a single listing for CNV (due to AMD, PM, or rare conditions – see also PSD Item 6.05 ranibizumab, March 2018 PBAC meeting). The PBAC also noted that appropriate coordination was in place to amend the MBS item for the codependent technology of OCT.

7.4 The PBAC considered that the nominated comparator of verteporfin photodynamic therapy (vPDT) is not appropriate to assess the cost-effectiveness of ranibizumab for this condition in this instance. The PBAC noted that, although vPDT (subsidised as a medical procedure through the Medical Benefits Schedule) is currently the only subsidised therapy for subfoveal CNV secondary to PM, the cost-effectiveness of verteporfin for the treatment of CNV due to PM has not been previously accepted by the PBAC. Further, the PBAC recalled that, at its November 2005 meeting, it did not recommend the listing of verteporfin for the treatment of CNV due to other macular diseases because of unacceptable cost-effectiveness. The PBAC agreed with the ESC that, in the absence of a treatment that has been determined to be cost-effective for this indication, sham injection (for no treatment) was the most appropriate comparator for assessing the cost-effectiveness of ranibizumab for the treatment of CNV due to PM. As such, the PBAC considered that the economic evaluation presented in the submission, claiming dominance of ranibizumab compared to vPDT was not directly informative.

7.5 The PBAC noted that the submission was based on two head-to-head randomised trials, RADIANCE and BRILLIANCE, comparing ranibizumab treatment guided by visual acuity stabilisation or disease activity to vPDT in adult patients with CNV secondary to PM. The PBAC noted that, for both trials, there was only 3 months of randomised comparative data available due to the majority of patients in the vPDT arms switching to ranibizumab at the end of month 3.

7.6 The PBAC noted that the mean differences in mean average change from baseline to Month 1 through Month 3 in best corrected visual acuity (BCVA) for ranibizumab over vPDT of 8.5 to 8.6 letters in the RADIANCE trial and [redacted] letters in the BRILLIANCE trial. The PBAC recalled that it previously recommended extending the listing of ranibizumab to include treatment of diabetic macular oedema (DME) on the basis of an improvement of 5 letters or more. The PBAC also recalled that it previously considered that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye will depend on the baseline visual acuity of the patient in both eyes and on the subsequent overall visual acuity during and after treatment. The PBAC accepted the submission's proposed minimally important clinical difference of at least 5 letters in BCVA based on the evidence presented, noting that mean BCVA at baseline was 55 letters and [redacted] letters in the RADIANCE

and BRILLIANCE trial respectively.

7.7 The PBAC therefore considered that the claim of superior efficacy over vPDT was reasonable. The PBAC also noted that data from Tan et al 2017 provided some support of the long-term safety and efficacy of ranibizumab.

7.8 The PBAC noted there was insufficient data to adequately evaluate the safety of ranibizumab compared with vPDT. However, the PBAC noted there were no major safety signals in the trials and that the adverse event profile of ranibizumab was consistent with its profile for current indications.

7.9 The PBAC noted that the mean number of ranibizumab injections per patient in both RADIANCE and BRILLIANCE trials was higher in the ranibizumab arm with retreatment guided by VA stabilisation (4.6 injections in both trials) compared with the ranibizumab arm with retreatment guided by disease stabilisation (RADIANCE 3.5 injections, BRILLIANCE [redacted] injections). The PBAC considered that in clinical practice, a mix of both methods may be used, which may result in a higher average number of ranibizumab injections compared with the trials. The PBAC also noted that, although the submission stated that [redacted]% of patients would receive an additional injection after the first year, no information was provided on how this estimate was derived beyond a statement that it was based on clinical expert opinion. Taken together with the lack of long-term data beyond 12 months, the PBAC considered there was uncertainty in the average number of ranibizumab injections for the treatment of CNV due to PM which would be administered in clinical practice.

7.10 The PBAC noted that the economic evaluation relied only on the RADIANCE trial, on the basis that the multicultural population (consisting of 40% Asian and 60% Caucasian patients) included in the trial is more likely to reflect the Australian population. The PBAC considered the exclusion of the BRILLIANCE trial from the economic analysis, on the basis that [redacted]% of the patients in the trial were Asian, was not justified noting there was no evidence that race was a treatment effect modifier. However, the PBAC also noted that the model was more sensitive to other assumptions than the selection of the trial basis for the model.

7.11 The PBAC considered the transition probabilities between visual acuity health states applied in the economic model to be uncertain because:

- The transition probabilities for the vPDT arm in the first 12 months were estimated from the 15 patients in the vPDT arm who did not switch to ranibizumab treatment within the first 12 months. The majority of these patients (13/15) did not meet the re-treatment criteria guided by disease activity and did not receive any further treatment, and so were unlikely to be reflective of patients receiving vPDT in the absence of treatment with ranibizumab.
- The same yearly transition probabilities were assumed beyond Month 12 for the entire time horizon. These were estimated using short term probabilities

observed from the RADIANCE trial assuming a constant rate for both improving and worsening beyond Month 12.

However, the PBAC considered that the estimated transition probabilities beyond Month 12 were likely to represent a conservative approach in the modelling as the overall effect of the extrapolated transition probabilities resulted in a net decline in visual acuity over time in both arms of the model. By comparison, the PBAC noted that the results of long-term outcomes of ranibizumab treatment of myopic CNV in east-Asian patients from the RADIANCE trial reported in Tan et al (2017) of +10.4 ±22.3 letters at 24 months and +16.3 ±18.7 letters at 48 months.

7.12 The PBAC agreed with its ESC that the submission's approach to include both cost of falls and cost of blindness in the economic evaluation represented a double counting the cost of falls. The PBAC recalled that, at its July 2014 consideration of ranibizumab for the treatment of RVO and DME, it had accepted a base case in both instances which did not include the cost of falls. However, the sensitivity analyses showed that the estimated consequences for fall cost offsets had little effect on varying the ICER results.

7.13 The PBAC considered that, given the issues regarding the use of vPDT as a comparator in the economic evaluation (see paragraph 7.4 above) and the absence of any other treatment which has been assessed to be cost-effective for this indication, it would be informative to estimate the cost-effectiveness of ranibizumab for this indication using the vPDT arm as a proxy for sham injection (no treatment) by removing the costs associated with the administration of vPDT from the model. However, the PBAC considered that removing costs associated with vPDT treatment while assuming the same treatment effect and healthcare resources originally modelled for vPDT, was likely to overestimate health outcomes associated with sham injection (no treatment) and was therefore likely a conservative approach.

7.14 The PBAC noted that removing costs associated with administration of vPDT and the cost of falls from the model resulted in an ICER of less than $15,000 per QALY gained. The PBAC noted that the further sensitivity analyses provided by its ESC (see Table 14), which tested the effect of the number of ranibizumab injections and duration of therapy per patient on the overall cost-effectiveness of ranibizumab for the treatment of CNV due to PM, indicated that the model was sensitive to the overall number of ranibizumab injections per patient. When the average number of ranibizumab injections per patient applied in the model was increased to the average number of injections of ranibizumab per patient administered in treating AMD found in the June 2015 DUSC utilisation review (8.4 injections in the first year and 7.1 injections in subsequent years), the ICER increased substantially to more than $200,000 per QALY gained. The PBAC therefore considered that ranibizumab would not be cost-effective for the treatment of CNV due to PM if the number of injections per year approached those similar to the number of injections of ranibizumab for the treatment of AMD. However, the PBAC considered that an ICER of more than $200,000 per QALY was representative of a 'worst-case' scenario and

that, based on the available evidence, the number of injections in clinical practice would likely be lower. The PBAC considered that any risk associated with uncertainty around the number of ranibizumab injections may be adequately managed if the requested indication was included in the existing Deed of Agreement for ranibizumab used in AMD.

7.15 The PBAC considered that, although it was possible that a proportion of patients with subfoveal CNV due to PM are currently receiving PBS-subsidised VEGF inhibitor therapy outside their PBS restrictions (i.e. for subfoveal CNV due to AMD), it was not justified to include cost offsets for this utilisation without any substantive evidence quantifying the extent of this occurrence.

7.16 The PBAC considered that the estimated financial implications (without cost offsets due to use of PBS-listed drugs outside their PBS restrictions) of less than $10 million in Year 6 was reasonable and there was a low risk of use outside the proposed restriction. The PBAC advised that the inclusion of the extended indication as part of the existing Deed of Agreement for CNV, [redacted], was essential to containing the overall cost of ranibizumab in CNV. [redacted] As such, the PBAC considered that an alternative arrangement [redacted] would also be appropriate.

7.17 The PBAC noted that it had also made a positive recommendation for the listing of ranibizumab due to rare causes. The PBAC considered that it may be appropriate to amend the existing restriction for ranibizumab for the treatment of subfoveal CNV due to AMD to include these two additional patient populations if the indications were included in the existing Deed of Agreement for CNV.

7.18 The PBAC confirmed that ranibizumab is not suitable for prescribing by nurse practitioners.

7.19 The PBAC confirmed that the Early Supply Rule should not apply to ranibizumab.

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

Outcome:
Recommended

8 Recommended listing

8.1 Extend the existing listing to include:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
RANIBIZUMAB 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	Lucentis® Novartis Australia Pty. Ltd.
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe			

Condition:	Subfoveal choroidal neovascularisation
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	The condition must be due to pathologic myopia, AND Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date], AND The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, AND The treatment must be the sole PBS-subsidised therapy for this condition.
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 Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form and a copy of the optical coherence tomography or

	fluorescein angiogram report. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice	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. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Special Pricing Arrangements apply. Pharmaceutical benefits that have the form ranibizumab 0.165 mL injection syringe and pharmaceutical benefits that have the form ranibizumab 0.23 mL injection vial are equivalent for the purposes of substitution.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RANIBIZUMAB 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	Lucentis®	Novartis Australia Pty. Ltd.
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe				

Condition:	Subfoveal choroidal neovascularisation
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined

Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	The condition must be due to pathologic myopia, AND The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, AND The treatment must be the sole PBS-subsidised therapy for this condition.
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 Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report. A telephone application must be made following submission by facsimile of a copy of a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	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. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Special Pricing Arrangements apply. Pharmaceutical benefits that have the form ranibizumab 0.165 mL injection

	syringe and pharmaceutical benefits that have the form ranibizumab 0.23 mL injection vial are equivalent for the purposes of substitution.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RANIBIZUMAB 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	Lucentis®	Novartis Australia Pty. Ltd.
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe				

Condition:	subfoveal choroidal neovascularisation
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	The condition must be due to pathologic myopia, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye
Administrative Advice	Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Special Pricing Arrangements apply. Pharmaceutical benefits that have the form ranibizumab 0.165 mL injection syringe and pharmaceutical benefits that have the form ranibizumab 0.23 mL injection vial are equivalent for the purposes of substitution.