

## 6.05 RANIBIZUMAB, 2.3 mg/0.23 mL, 0.23 mL vial and 1.65 mg/0.165 mL, pre-filled syringe, Lucentis<sup>®</sup>, 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 the treatment of visual impairment caused by rare choroidal neovascularisation (CNV), which covers CNV secondary to conditions other than age-related macular degeneration (AMD) or pathologic myopia (PM). For convenience, CNV caused by conditions other than AMD or PM is referred to as ‘rare CNV’. 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 the treatment of CNV secondary to 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 sham treatment in patients with CNV due to causes other than AMD or PM.

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

Component	Description
Population	Patients with visual impairment due to rare choroidal neovascularisation (CNV). The requested restriction is for subfoveal CNV not due to age-related macular degeneration or pathologic myopia.
Intervention	Ranibizumab solution for intravitreal injection.
Comparator	Sham treatment.
Outcomes	Best corrected visual acuity (BCVA) <sup>a</sup> , quality of life, safety.
Clinical claim	In patients with rare choroidal neovascularisation, ranibizumab is superior to sham therapy in terms of efficacy and quality of life, and is non-inferior to sham therapy in terms of safety.

<sup>a</sup> The primary outcome was change in BCVA from baseline to the end of month 2.

Source: Table 1.1-1, p23 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 due to rare causes.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, restriction, manner of administration, form	Maximum quantity	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
RANIBIZUMAB				Lucentis <sup>®</sup>
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe	1	2	\$1,149.44 (published price) \$ [REDACTED] <sup>a</sup> (effective price)	Novartis Australia Pty. Ltd.
2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	\$1,149.44 (published price) \$ [REDACTED] <sup>a</sup> (effective price)	

<sup>a</sup> Based on the effective dispensed price for maximum quantity for ranibizumab for CNV due to age-related macular degeneration, as of 1 January 2018.

Public Summary Document – March 2018 PBAC Meeting

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Subfoveal choroidal neovascularisation
<b>PBS Indication:</b>	Subfoveal choroidal neovascularisation
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist <i>or in consultation with an ophthalmologist.</i>
<b>Clinical criteria:</b>	The condition must <del>not</del> be due to <i>causes other than</i> age-related macular degeneration (AMD) <del>and</del> 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.
<b>Prescriber Instructions</b>	<i>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.</i>
<b>Administrative Advice</b>	<i>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 <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Special Pricing Arrangements apply. Pharmaceutical benefits that have the form ranibizumab 0.165 mL injection syringe</i>

	<i>and pharmaceutical benefits that have the form ranibizumab 0.23 mL injection vial are equivalent for the purposes of substitution.</i>
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Subfoveal choroidal neovascularisation
<b>PBS Indication:</b>	Subfoveal choroidal neovascularisation
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist <i>or in consultation with an ophthalmologist.</i>
<b>Clinical criteria:</b>	The condition must <del>not</del> be due to <i>causes other than</i> age-related macular degeneration (AMD) <del>or</del> and pathologic myopia (PM) AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously been granted an authority prescription for the same eye
<b>Administrative Advice</b>	<i>Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i> <i>Special Pricing Arrangements apply.</i> <i>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.</i>

- 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 PBS listing of ranibizumab for the treatment of subfoveal CNV due to causes other than AMD or PM. The TGA indication is for the treatment of visual impairment due to CNV, 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 38% of patients in the key trial had juxtafoveal or extrafoveal CNV lesions, and the economic analysis was based on the results in the entire trial population. 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 rare CNV 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 indication. (See Financial Management – Risk Sharing Arrangements, below for more detail).
- 2.7 The submission did not request a grandfather clause for patients currently receiving compassionate supply of ranibizumab through the sponsor. The requested restriction does not prevent the use of PBS subsidised ranibizumab in these patients.
- 2.8 The current MBS descriptor for optical coherence tomography (OCT) (MBS item 11219) does not include determining whether the requirements for access to initial treatment with ranibizumab for rare CNV 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 for the treatment of visual impairment due to CNV in August 2017.

#### ***Previous PBAC consideration***

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

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

### **4 Population and disease**

- 4.1 CNV 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.
- 4.2 Aside from AMD and PM, other causes of CNV are considered rare due to low incidence and prevalence. The submission proposed ranibizumab for the treatment of rare CNV. The submission stated that the most commonly associated conditions are angioid streaks (AS), central serous chorioretinopathy (CSC), inflammatory

retinopathies, idiopathic CNV without any apparent ocular or systemic disease, and other causes such as trauma, tumours, and retinal or macular dystrophies.

- 4.3 Ranibizumab is a vascular endothelial growth factor (VEGF) inhibitor. VEGF has been shown to play a critical role in the molecular pathogenesis of CNV, regardless of the primary aetiology. Stimulation of VEGF signalling is critical for the development of CNV, and VEGF is required for continued growth and leakage of the neovascularisation.\*

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

## 5 Comparator

- 5.1 The submission nominated sham therapy as the main comparator, on the basis that there is no established standard of care that is efficacious for the full range of patients covered under rare CNV.
- 5.2 Ranibizumab and verteporfin photodynamic therapy (vPDT) are the only TGA registered drugs for the treatment of CNV due to causes other than AMD or PM. In November 2005, the PBAC did not recommend verteporfin for CNV due to macular diseases other than AMD because of the unacceptably high incremental cost per extra quality-adjusted life year (QALY) gained of more than \$200,000, in comparison with placebo (Section 12, verteporfin Public Summary Document (PSD), November 2005 PBAC meeting).
- 5.3 In the absence of an alternative treatment that has been determined to be cost-effective for this indication, the ESC agreed with the submission that no active CNV treatment (represented by sham injection in the trial evidence) is the most relevant comparator for assessing clinical and cost-effectiveness of ranibizumab for the treatment of rare CNV. The PBAC considered that sham injection (as a proxy for no treatment) is the appropriate comparator to assess the clinical and cost-effectiveness of ranibizumab for the treatment of rare CNV.

*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

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\* Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res.* 2015; 49:67-81.

College of Ophthalmologists in support of a listing of ranibizumab for the treatment of patients with rare CNV.

### Clinical trials

6.3 The submission was based on one head-to-head randomised trial (MINERVA) comparing ranibizumab (N=119) with sham therapy (N=59) in patients with rare CNV.

6.4 Details of the trial 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
MINERVA	Clinical Study Report: A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven choroidal neovascularization.	March 2016
	Lai TYY, Staurenghi G, et al. Efficacy and safety of ranibizumab for the treatment of choroidal neovascularization due to uncommon cause: Twelve-month results of the MINERVA study.	<i>Retina</i> . Published ahead of print.
	Hykin P, et al. Efficacy and safety of ranibizumab 0.5 mg in adult patients with visual impairment due to choroidal neovascularization associated with rare diseases: 12-month results of the MINERVA study.	<i>Ophthalmologica</i> 2016; 236: 11-12.
	Gilhotra J, et al. Efficacy and safety of ranibizumab 0.5 mg in adult patients with visual impairment due to choroidal neovascularization associated with rare diseases: 12 month results of the MINERVA study.	<i>Clinical and Experimental Ophthalmology</i> 2016; 44 (supplement S1): 123-4.

Source: Table 2.2-1, p37 of the submission.

6.5 The key features of the direct randomised trial 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
<b>Ranibizumab vs. sham</b>						
MINERVA	178	R, DB 2 months <sup>a</sup>	Low	Rare CNV	Mean BCVA change from baseline to Month 2 of the study eye <sup>b</sup>	Used (only data from ranibizumab arm are used)

BCVA = best corrected visual acuity; CNV = choroidal neovascularisation; DB=double blind; R = randomised.

<sup>a</sup> Comparative data for ranibizumab versus sham were only available for 2 months. The final study assessment was performed at the end of 12 months.

<sup>b</sup> The primary outcome used efficacy assessments collected at baseline, and the end of month 1 and month 2, and was analysed using a mixed-effect repeated measures model.

Source: Sections 2.3 and 2.4, pp38-52 of the submission.

6.6 The ESC noted a publication in January 2018 of findings from the PROMETHEUS trial<sup>†</sup> (sponsored by Novartis). The ESC noted that, while the purpose of the trial was to

<sup>†</sup> Staurenghi, G. Lai, T.Y.Y. Mitchell P. Wolf S. Wenzel A. Li, J. Bhaumik, A. and Hykin, P.G. 2018 'Efficacy and Safety of Ranibizumab 0.5 mg for the Treatment of Macular Edema Resulting from Uncommon Causes' *Ophthalmology* DOI · 10.1016/j.ophtha.2017.12.002

evaluate the efficacy and safety of ranibizumab in adult patients with macular edema (ME) resulting from any cause other than diabetes, retinal vein occlusion, or neovascular age-related macular degeneration, the study design for PROMETHEUS including the sample size calculation was very similar to that of the MINERVA trial and the two trials were run concurrently (MINERVA was initiated in September 2013 and completed in November 2015; PROMETHEUS was initiated in October 2013 and completed in September 2015). While patients with CNV do not appear to have been specifically excluded from the PROMETHEUS trial, Staugrenghi et al, 2018 does not report whether any patients had CNV. The incremental gain at 2 months in mean the best corrected visual acuity (BCVA) for ranibizumab vs sham was considerably less than the incremental gain in the MINERVA trial (2.8 letters in PROMETHEUS vs 9.94 letters in MINERVA). The sponsor was therefore requested to confirm the extent of overlap if any between the patient populations in the MINERVA and PROMETHEUS trials. The PBAC noted the pre-PBAC response suggested that there is unlikely to be a large overlap given the vision gains in PROMETHEUS were similar to DMO trials (RESTORE) which excluded CNV due to any cause.

- 6.7 In the Minerva trial, at Month 2 (2 months  $\pm$  7 days after the baseline visit), all patients randomised to the sham arm were permitted to switch to open-label treatment with ranibizumab. This treatment switching option was pre-specified in the trial protocol. From Month 2 to Month 11 (11 months  $\pm$  7 days), patients received monthly monitoring and ranibizumab injections as needed, based on evidence of disease activity (judged clinically or based on morphology/imaging). The last study assessment was performed at Month 12 (12 months  $\pm$  7 days). The PSCR argued that allowing the sham injection arm of the trials to access ranibizumab at Month 2 was ethical and logical, reflecting the clinical value of ranibizumab in these patients.
- 6.8 Fifty-two out of 59 patients randomised to sham arm received at least one ranibizumab injection by Month 12. The seven patients in the sham injection arm who did not receive any ranibizumab injections were also switched to ranibizumab on an as-needed basis but, at each monthly assessment, either had no evidence of disease activity (i.e. did not meet the criteria for re-treatment) or had discontinued all study treatment. Consequently, comparative data for ranibizumab versus sham injection were only available up to Month 2.
- 6.9 Overall, the risk of bias was low over the 2 month masked, comparative period of the trial. However, although patients and investigators remained masked to original treatment allocation, from Month 2 to Month 12 the trial was open-label and uncontrolled, with potential for both performance and assessment bias, especially for subjective outcomes. The ESC acknowledged the contamination of the trial results comparing ranibizumab with sham after Month 2 when the majority of patients randomised to sham were switched to ranibizumab treatment.

- 6.10 The trial included adult patients with one of the following CNV lesions 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.
- 6.11 One eye was selected as the study eye. If both eyes were eligible, the eye selected as the study eye was the one the investigator deemed to be more appropriate for study treatment and the study, based on the most appropriate active CNV lesion characteristics, in addition to visual impairment. All visual acuity outcomes in the trial were assessed in the study eye.
- 6.12 Randomisation was stratified by type of underlying ocular pathophysiologic mechanism (angioid streaks vs other). The study population in MINERVA included patients with the following underlying aetiologies of CNV: angioid streaks (15.2%), inflammatory retinochoroidopathy (15.7%), CSC (12.9%), idiopathic chorioretinopathy (35.4%), and miscellaneous (20.8%). It was not clear whether the trial population was representative of the target Australian patient population with regard to the relative frequencies of the multiple underlying aetiologies of rare CNV. The ESC noted that the small number of patients in the trial limited any comparisons to determine whether the trial population was reflective of the Australian patient population but, given the results appeared similar across the different causes of rare CNV, this was not a major concern.
- 6.13 The submission proposed a difference of at least 5 letters in the BCVA as the minimal clinically important difference between the ranibizumab and sham injection groups. 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 has previously accepted that an improvement in visual acuity of 10 letters represented a clinically important difference, and 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).

### ***Comparative effectiveness***

- 6.14 The results for the primary outcome in MINERVA, the change in BCVA of the study eye from baseline to Month 2, are summarised in the table below.

**Table 4: Average change in BCVA of the study eye from baseline to Month 2, FAS (observed)<sup>a</sup>**

BCVA (letters)	Ranibizumab N=118	Sham injection N=57
<b>Primary analysis, FAS (observed)</b>		
Baseline, mean (SD)	62.3 (15.01)	61.4 (14.20)
Average change from baseline, LS mean (95% CI)	9.5 (7.6, 11.4)	-0.4 (-2.8, 1.9)
Difference in LS mean, ranibizumab vs sham (95% CI) p-value	<b>9.94 (6.97, 12.91)</b> <b>&lt;0.001</b>	
<b>Sensitivity analyses</b>		
FAS (MV-LOCF), difference in LS mean (95% CI)		
Per protocol set, difference in LS mean (95% CI)		

BCVA = best corrected visual acuity; CI = confidence interval; FAS = full analysis set; LS = least squares; MV-LOCF = mean value last observation carried forward; SD = standard deviation.

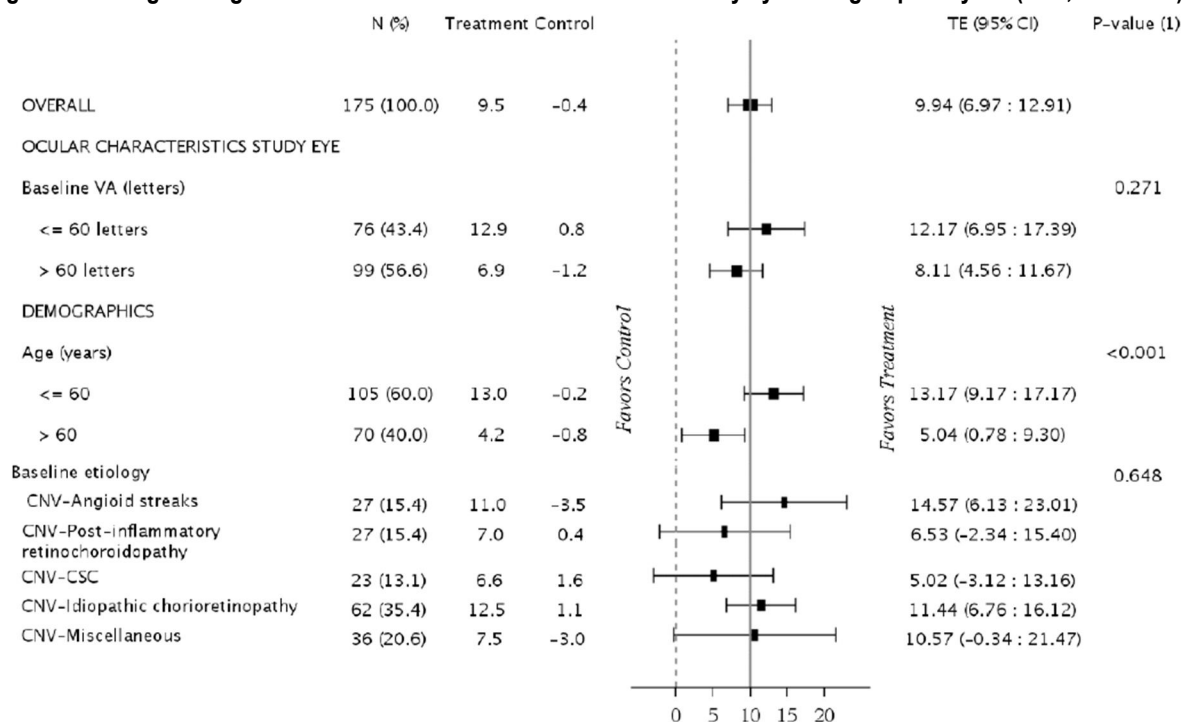
<sup>a</sup> The primary analysis was performed in the FAS (observed). One patient in the ranibizumab arm and 2 patients in the sham injection arm were not included in the analysis as they did not have BCVA values recorded at either Month 1 or Month 2.

Source: Table 2.4-3 p46 and Table 2.5-1 p53 of the submission; Section 11.4.1.1 p106, Table 14.2-1.6 p243, Table 14.2-1.2 p236 and Table 14.2-1.3 p237 of the Clinical Study Report (CSR).

6.15 Ranibizumab was statistically superior to sham injection in terms of the average change in BCVA of the study eye from baseline to Month 2. The results of the sensitivity analyses performed, firstly, with imputation of missing observations and, secondly, based on the per protocol analysis set, were consistent with the primary analysis. The magnitude of the treatment effect over the first 2 months of treatment was likely to be clinically meaningful. The ESC considered the benefit observed in patients in the ranibizumab arm at Month 2 to be clinically significant also noting that >40% of patients in the ranibizumab treatment arm gained  $\geq 10$  letters or reached 84 letters at Month 2.

6.16 Subgroup analyses for the primary endpoint are presented in the figure below.

Figure 1: Average change in BCVA from baseline to Month 2 of the study eye – subgroup analyses (FAS, observed)



BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularisation; CSC = central serous chorioretinopathy; FAS = full analysis set; TE = treatment effect; VA = visual acuity.

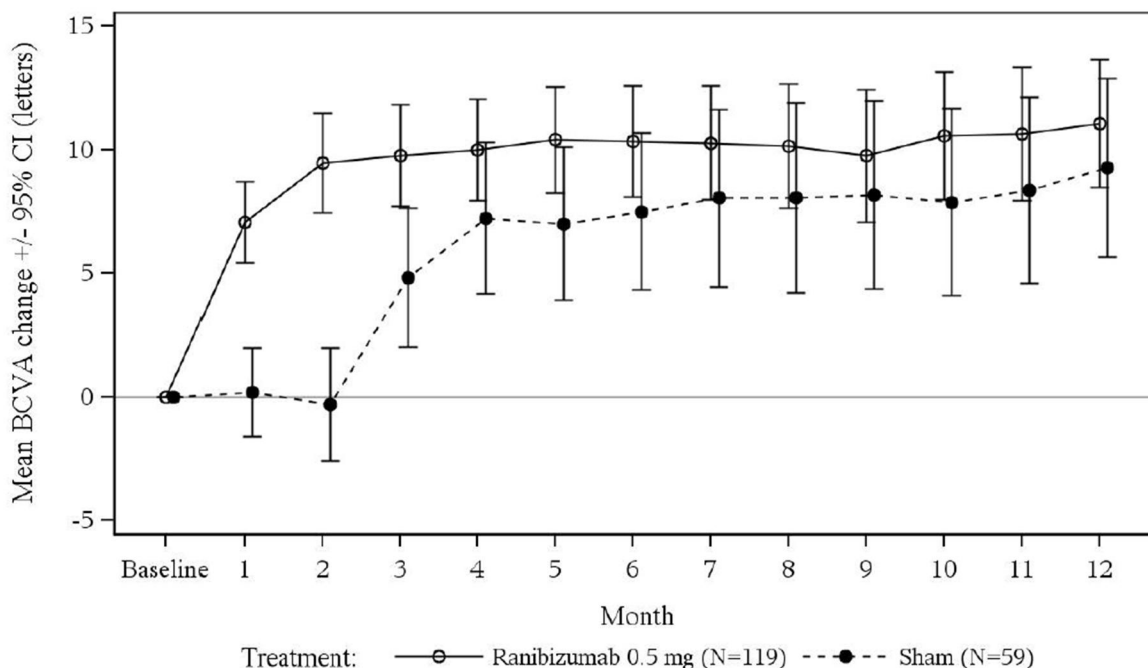
Note: the treatment effect is the difference in adjusted least squares mean (letters).

(1) p-value is of the interaction between the subgroup and treatment.

Source: Figure 2.5-1, p54 of the submission; Figure 11-2 p107 of the CSR.

- 6.17 Age is reported to be a statistically significant treatment effect modifier, with patients aged  $\leq 60$  years having a significantly higher treatment effect with ranibizumab versus sham injection, compared to patients aged  $>60$  years.
- 6.18 The submission stated that, in the CNV baseline aetiology subgroups, the treatment effect for ranibizumab compared with sham (difference in adjusted least squares mean between groups) to Month 2 ranged from 5.0 letters (95% confidence interval (CI): -3.1, 13.2) to 14.6 letters (95% CI: 6.1, 23.0),  $p=0.65$ , demonstrating that the aetiology of the CNV did not appear contributory to the overall positive result. These subgroup analyses were insufficiently powered to accurately determine the treatment effect for each aetiology, or to reliably detect any true difference in treatment effect between subgroups. However, the ESC noted that the CNV baseline aetiology subgroup analyses were suggestive of a treatment benefit with ranibizumab for all causes of rare CNV though the patient numbers were small.
- 6.19 The mean change from baseline in BCVA of the study eye over time is presented in Figure 2 below.

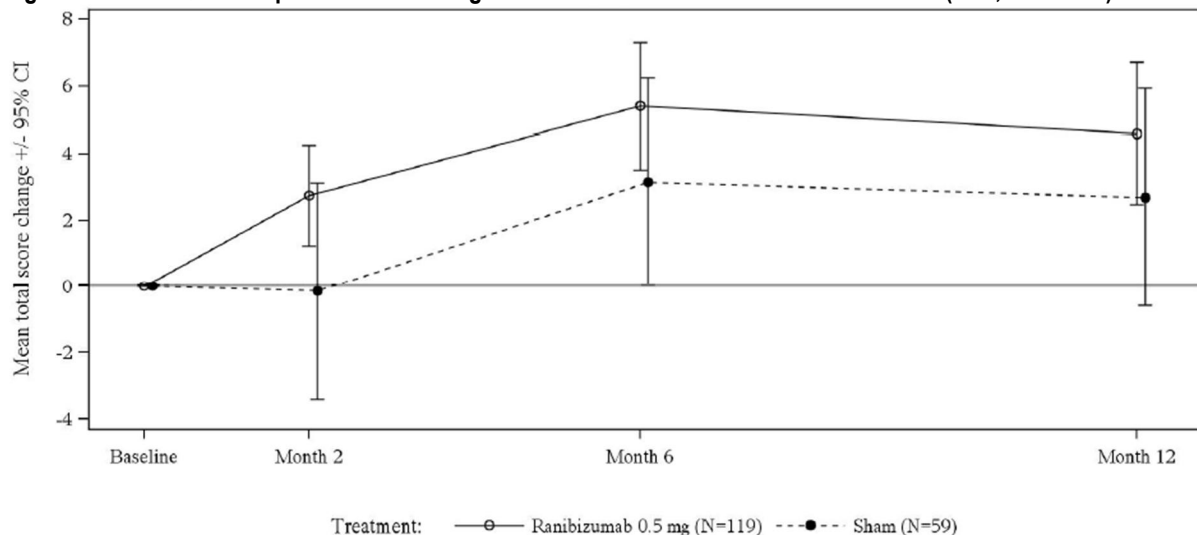
Figure 2: Mean change from baseline in BCVA of the study eye over time in MINERVA (FAS, observed)



BCVA = best corrected visual acuity; CI = confidence interval; FAS = full analysis set.  
 Source: Figure 2.5-2, p55 of the submission.

- 6.20 The submission claimed that a continuous numerical improvement in BCVA of the study eye was observed up to Month 12, and that a steady improvement in BCVA was also observed in the sham injection group following the allowance of open-label ranibizumab as of Month 2 in patients randomised to this arm. In both arms, the improvement in BCVA of the study eye plateaued after 3-4 months of ranibizumab treatment and was maintained to Month 12. The ESC considered that the improvement in mean BCVA change in the sham injection arm after month 2 was indicative of the treatment benefit with ranibizumab. However, it was noted that, after cross-over, the sham arm did not reach the same level of improvement as the ranibizumab arm and it was considered that this may suggest that earlier onset of treatment was better. The PBAC considered the wide confidence intervals signalled that there is insufficient evidence to support this conclusion.
- 6.21 The National Eye Institute Visual Function questionnaire 25 (NEI VFQ-25) was used to measure vision-targeted health-related quality of life in the trial. 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 Figure 3.

Figure 3: NEI-VFQ-25 composite score: change from baseline over the duration of the trial (FAS, observed)



CI = confidence interval; FAS = full analysis set; NEI VFQ = National Eye Institute visual function questionnaire.  
Source: Figure 2.5-3, p59 of the submission.

6.22 The submission stated that, although the difference in NEI VFQ-25 scores between the treatment arms were not statistically significant, there was a trend in favour of ranibizumab treatment. As for the other outcomes, comparative data for ranibizumab versus sham injection were only available to Month 2 of the trial. The clinical importance of the observed improvements in scores in patients receiving ranibizumab was not addressed in the submission.

### Comparative harms

6.23 Given the short duration of the comparative stage of the trial, and the low number of events in the relatively small trial population, the trial provided insufficient safety data to reliably determine the comparative safety of ranibizumab versus sham injection for the treatment of rare CNV.

6.24 The submission presented 12 month safety results for the subgroups of patients in the sham injection arm who did, and did not, receive ranibizumab after the end of the comparative period at Month 2. Subsequent to Month 2, the subgroup of patients in the sham treatment arm who did not receive ranibizumab were not a valid control group; these patients were permitted to switch to ranibizumab treatment on an as-needed basis but were either not considered to require treatment or had discontinued all study treatment.

6.25 Table 5 summarises the key adverse events (AEs) over the 12 month study period of the trial.

**Table 5: Summary of key adverse events up to Month 12 in MINERVA**

	Ranibizumab N=119	Sham with ranibizumab N=52	Sham without ranibizumab N=7
Any AE			
Ocular (study eye)	30 (25.2%)	22 (42.3%)	3 (42.9%)
Non-ocular	67 (56.3%)	25 (48.1%)	3 (42.9%)
Treatment related ocular AE (study eye)			
Related to ocular injection	15 (12.6%)	12 (23.1%)	1 (14.3%)
Related to study drug	2 (1.7%)	1 (1.9%)	0 (0.0%)
Treatment related non-ocular AE	0	0	1 (14.3%)
Serious AEs, n (%)	9 (7.6%)	4 (7.7%)	0
Study eye	0	0	0
Fellow treated eye	0	0	0
Fellow untreated eye	1 (0.8%)	0	0
Non-ocular	8 (6.7%)	4 (7.7%)	0
Discontinued study drug due to AE, n (%)	2 (1.7%)	0	1 (14.3%)
Study eye	0	0	1 (14.3%)
Non-ocular	2 (1.7%)	0	0

AE = adverse event

Source: Table 2.5-6, p61 of the submission; Table 14.3.1-3.6 p1022, Table 14.3.1-3.10 p 1026 and Table 14.3.1-3.13 p1030 of the CSR.

- 6.26 The submission stated that, over the 12 month study period, patients in the ranibizumab group experienced a lower frequency of ocular AEs compared to the sham with ranibizumab group ( $p=0.03$ ). Given that all patients randomised to sham injection were permitted to switch to ranibizumab treatment on an as-needed basis from Month 2 to Month 12, no comparison of the 12 month safety data between the treatment groups was possible.
- 6.27 The TGA clinical evaluator noted that, in spite of data showing minimal systemic absorption, the incidence of systemic ranibizumab-related AEs reported in the trial highlighted the requirement for monitoring of vascular events in this patient population.
- 6.28 The TGA clinical evaluator concluded that the treatment-related risks observed in MINERVA were consistent with the known safety profile of ranibizumab. The potential safety concerns with the use of ranibizumab relate to [REDACTED].  
[REDACTED] Further, because of the theoretical risk of arterial thromboembolic events with intravitreal VEGF inhibitors, relevant important potential risks are [REDACTED].  
[REDACTED].
- 6.29 The safety data were largely non-comparative. The short duration of the study and small patient population limit the ability to comment on the long term safety profile of ranibizumab for these conditions, some of which often require long term treatment. The ESC noted that the long term safety profile of ranibizumab is known for other indications and considered that the safety profile is unlikely to be significantly different in this heterogeneous population.

## Benefits/harms

6.30 A summary of the comparative benefits for ranibizumab over sham injection is presented in the table below. Due to the short duration of the comparative stage of the trial, and the low number of events in the relatively small number of patients, the trial provided insufficient comparative safety data for ranibizumab versus sham injection to allow a reliable comparison of harms.

**Table 6: Summary of comparative benefits for ranibizumab and sham injection**

Benefits							
Average change in BCVA of the study eye from baseline to Month 2							
Trial	Ranibizumab			Sham			Mean difference: Ranibizumab vs. sham (95% CI)
	N	LS mean $\Delta$ baseline (letters)	95% CI	N	LS mean $\Delta$ baseline (letters)	95% CI	
MINERVA	118	9.5	7.6, 11.4	57	-0.4	-2.8, 1.9	9.94 (6.97, 12.91)

BCVA = best corrected visual acuity; CI = confidence interval; LS = least squares;  $\Delta$  = change.

Source: Table 2.4-3 p46 and Table 2.5-1 p53 of the submission; Table 14.2-1.2 p236 and Table 14.2-1.3 p237 of the CSR.

6.31 On the basis of the direct evidence presented by the submission, the comparison of ranibizumab and sham injection resulted in approximately a 10 letter improvement in mean average change in BCVA of the study eye from baseline to Month 2. This improvement was likely to be clinically meaningful. The ESC noted that the mean BCVA at baseline was 62 letters in the MINERVA trial, with 70 letters being the legal driving level.

## Clinical claim

6.32 The submission described ranibizumab as superior in terms of effectiveness and non-inferior in terms of safety compared to sham injection in patients with rare CNV.

6.33 The evidence presented in the submission supported the conclusion that ranibizumab is superior to sham injection in terms of the mean average improvement in BCVA of the study eye from baseline to Month 2. The improvement in BCVA in patients randomised to ranibizumab was maintained over Month 2 through Month 12. However, there were no comparative effectiveness data for ranibizumab versus sham injection beyond 2 months, and the submission did not present any data on the long-term effectiveness of ranibizumab beyond the 12 month duration of the trial. The ESC considered that the claim of superior efficacy compared to sham injection was supported for the first two months of treatment.

6.34 The pre-PBAC Response stated that Mimoun 2017<sup>†</sup> reported that in 72 patients with CNV due to pseudoxanthoma elasticum, the most common cause of AS, treated with ranibizumab, BCVA was stable in 52.6% and improved ( $\geq 15$  letters) in 15.8% of

<sup>†</sup> Mimoun G, Ebran JM, et al. Ranibizumab for choroidal neovascularization secondary to pseudoxanthoma elasticum: 4-year results from the PIXEL study in France. Graefes Arch Clin Exp Ophthalmol. 2017; 255 (8):1651-60.

patients at 2.4 years follow up. The pre-PBAC Response also stated that in another case series (Tilleul et al 2016<sup>§</sup>) of 27 patients with AS, at the end of 4-year follow-up, BCVA was stabilised or improved in 62.9% of eyes. The PBAC noted that, although these studies are not representative of all aetiologies of rare CNV, the data provided some support of the long term efficacy of ranibizumab. The PBAC considered that the claim of superior efficacy over sham injection was reasonable.

- 6.35 The claim that ranibizumab is non-inferior to sham injection in terms of safety was not directly supported. Due to the short duration of the comparative stage of the trial, and the low number of adverse events over this period, the trial provided insufficient data to reliably determine the comparative safety of ranibizumab versus sham injection for the treatment of rare CNV. However, the safety profile of intravitreal ranibizumab in patients with rare CNV was consistent with that observed in other indications. The ESC considered that, although there was insufficient data to support a claim of non-inferior safety, there were no new safety signals with use of ranibizumab in rare CNV. The PBAC considered that, based on the available data, it was reasonable to accept that the safety profile of ranibizumab in this indication is consistent with its safety profile for its other indications.

### ***Economic analysis***

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

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<sup>§</sup> Tilleul J, Mimoun G, Querques G, Puche N, Zerbib J, Lalloum F, Srour M, Souied EH. Intravitreal Ranibizumab for Choroidal Neovascularisation in Angioid Streaks: Four-Year Follow-up. *Retina*. 2016;36(3):483-91.

**Table 7: 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 2 months. A 5 year time horizon and a lifetime horizon were tested in sensitivity analyses.
Outcomes	LYG and QALYs
Methods used to generate results	Markov cohort expected value analysis
Health states	[REDACTED]
Cycle length	1 month
Transition probabilities	For Year 1, transition probabilities for the ranibizumab arm were sourced from the key trial (MINERVA). In the no active treatment arm, it was assumed that patients remain in the same BCVA health state in Year 1. Transition probabilities for the subsequent years were assumed to be constant over the entire model time horizon. The long term transition probabilities for the ranibizumab arm were extrapolated from within trial data, assuming the probability of worsening being the average of the probability of worsening in Month 3-12 of the trial; and the probability of improving being 50% of the average probability of improvement in Month 3-12 of the trial. For the no active treatment arm, a constant probability of worsening, consistent with the ranibizumab arm was applied. No improvement of BCVA was assumed for this arm.

LYG = life years gained; QALY = quality-adjusted life years; ETDRS = Early Treatment diabetic Retinopathy Study; VA = visual acuity; BCVA = best corrected visual acuity.

Source: Table 3.1-1, p81 of the Submission.

6.37 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 incremental cost effectiveness ratios (ICERs) for each scenario as well as a weighted ICER.

6.38 The model did not include the cost or quality of life impact of treatment-related adverse events. This may not be reasonable, particularly when comparing with no active treatment. There were very limited comparative safety data available from the trial.

6.39 The transition probabilities beyond Month 12 between the BCVA health states were highly uncertain. The submission assumed constant transition probabilities beyond Month 12 for the entire model time horizon. These long-term transition probabilities for the ranibizumab arm were estimated using the short term probabilities observed from MINERVA under two main assumptions:

- The probability of moving to a worse BCVA health state beyond Month 12 was calculated as being the average probability of deterioration in VA in Month 3-12 of the trial;

- The probability moving to an improved BCVA health state beyond Month 12 was calculated as being 50% of the average probability of improvement in VA in months 3-12 of the trial.

The long term transition probabilities extrapolated from trial data were based on assumptions, for which the submission did not provide adequate justifications. The PSCR argued that some individual studies reported the long-term outcome for small groups of patients with CNV due to miscellaneous aetiologies and overall showed that CNV is associated with an increased risk of blindness and evidence from seven studies showed that 8% to 50% of patients with the condition were legally blind after a mean follow-up ranging from 2.5 to 9 years. The ESC noted these studies reported results for various indications, some of which were not consistent with the proposed PBS population, with varying lengths of follow up and that none of the studies identified related to the larger subgroups in MINERVA (e.g. CNV due to angioid streaks, idiopathic choroidopathy) on which the efficacy data is based.

The ESC considered the lack of long-term efficacy data beyond 12 months (compared with a 10 year time horizon), and utilisation of transition probabilities based on assumptions (beyond 12 months for the ranibizumab arm and for the entire time horizon for the sham arm) rendered the economic analysis to be highly uncertain. The PBAC considered that the extrapolated transition probabilities were likely to be conservative given the net decline in visual acuity over time in both arms of the model.

- 6.40 In the no active treatment arm, the submission assumed that patients would stay in the same health state as baseline in the first year. From Month 13, it was assumed that patients could transit to a worse VA state with a transition probability being the same as that in the ranibizumab arm, while assuming no improvement in VA health state. The transition probabilities applied in the no active treatment arm, and consequently the incremental treatment effect of ranibizumab versus no active treatment, were not based on evidence of treatment with sham nor the natural history of the disease. Further, the transition probabilities between VA health states were assumed to be the same for patients treated in the BSE or WSE. The ESC considered this was inappropriate and unlikely to reflect the true cost-effectiveness of patients treated in either their BSE or WSE.
- 6.41 In the model, although it was assumed that there were no changes in VA health states in the no active treatment arm in the first 12 months, ██████% of patients treated in the WSE in the no active treatment arm were assumed to have their treated eyes become the BSE at Month 12. This is not reasonable and biased the results of the economic model in favour of ranibizumab (the ICER increases from the base case of less than \$15,000/QALY to \$15,000/QALY - \$45,000/QALY when this favourable assumption is removed).

- 6.42 The average number of injections of ranibizumab per treated eye was uncertain given the lack of long term data (beyond the 12 month trial), the considerable variation in the number of treatments across aetiology subgroups as observed from MINERVA and the lack of data for the distribution of underlying aetiologies among the rare CNV patients in Australian clinical practice. The submission stated that the assumption of one additional injection of ranibizumab in Year 2 was based on expert opinion. The submission did not provide any detail on number and types of experts from which this estimate is derived or whether they reflected the population of ophthalmologists who would be treating rare CNV.
- 6.43 Each BCVA health state was assigned a utility weight dependent on whether the treated eye was the patient’s BSE or WSE, consistent with the previous ranibizumab submissions. For the bilateral treatment model, utility values for better-seeing eye were applied. The utility weights applied in the model are consistent with the evaluator ‘scenario 1’ utility values from the July 2014 ranibizumab submissions for DME and RVO. PBAC has previously noted the fundamental misalignment between the design of the model based on treated eye VA and overall patient utilities. The PBAC stated that the attempt to adjust for VA across both eyes for the purpose of mapping utilities did not address the fundamental misalignment in the model (paragraph 3.6, ranibizumab for DME PSD, July 2014 PBAC meeting). PBAC also considered that, as VA is influenced mostly by the better-seeing eyes, the potential for utility differences to occur is influenced by the proportions of better and worse seeing eyes are treated.
- 6.44 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 were consistent with those used in the previous ranibizumab submissions for both DME and RVO. The PBAC has 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 estimated more blindness in the no active treatment arm than in the ranibizumab arm, the cost of blindness contributed substantially to the cost-offsets and has underestimated the incremental cost of ranibizumab compared with no active treatment.
- 6.45 The key drivers of the model are summarised below.

**Table 8: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation	Constant transition probability over the entire model time horizon	High, favours ranibizumab
Time horizon	10 years	High, favours ranibizumab
The average number of ranibizumab injections per eye	5.8 injections in the first year based on MINERVA, one injection in Year 2 and no more injections thereafter based on expert opinion.	Moderate, favours ranibizumab
Cost of blindness	Cost of blindness associated with VA4 in addition to cost of fall	Moderate, favours ranibizumab

Source: compiled during the evaluation based on Sections 3.4, 3.6 and 3.9 of the submission.

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

**Table 9: Presentation of the stepped economic evaluation (weighted)**

	Ranibizumab	No active treatment	Incremental
<b>Step 1 – trial based analysis</b>			
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Mean change in BCVA at month 12	[REDACTED]	[REDACTED]	[REDACTED]
Cost per additional letter gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
<b>Step 2 – Cost utility analysis at Month 12 including drug cost only</b>			
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Cost per QALY gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
<b>Step 3 – Cost utility analysis at Year 10 including administration and monitoring costs</b>			
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Cost per QALY gained	[REDACTED]	[REDACTED]	\$ [REDACTED]
<b>Step 4 – Cost utility analysis at Year 10 including all costs</b>			
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Cost per QALY gained	[REDACTED]	[REDACTED]	\$ [REDACTED]

BCVA = best correct visual acuity; QALY = quality-adjusted life year

Note: An error was identified in the model where by the QALY gain for patients treated bilaterally was calculated by adding the QALY gain from the patients treated unilaterally in their WSE to those treated in their BSE. This has been corrected so that only the QALY gain for the BSE has been included. Results presented in this table in the submission were inconsistent with the results provided in other tables, and the results provided in EconomicModel\_Ranibizumab\_CNV.xlsx, Results sheet.

Source: Compiled during the evaluation based on analyses presented in Table 3.8-2; p92 Section 3 of the submission, using corrected results from EconomicModel\_Ranibizumab\_CNV.xlsx.

6.47 The results of the economic evaluation indicated that extrapolation from 12 months to 10 years (including drug costs only) reduced the ICER substantially, from over \$200,000/QALY to \$15,000/QALY - \$45,000/QALY. As noted above, the long term transition probabilities were highly uncertain given that the assumed constant transition probability over the entire model time horizon have not been adequately justified. Although the submission performed some sensitivity analyses using the long term transition probabilities sourced from literature, these analyses were of limited value, given that these transition probabilities were for different clinical indications and the number of ranibizumab injections were not comparable.

6.48 Sensitivity analyses indicated that the model is most sensitive to the time horizon, the number of ranibizumab injections and the cost associated with blindness. The key sensitivity analyses are presented below.

**Table 10: Results of key sensitivity analyses**

Parameter	Result	Base case value	Tested value or range	Rani	No active treatment	Incr.
<b>Base case</b>						
	Costs			\$ [redacted]	\$ [redacted]	\$ [redacted]
	QALYs			[redacted]	[redacted]	[redacted]
	Cost per QALY					\$ [redacted]
<b>Structural uncertainty</b>						
Model duration	Costs	10 years	5 years	\$ [redacted]	\$ [redacted]	\$ [redacted]
	QALYs			[redacted]	[redacted]	[redacted]
	Cost per QALY					\$ [redacted]
<b>Parameter uncertainty</b>						
Average number of ranibizumab treatments	Costs	Year 1 – 5.80 Year 2 – 1.00	Year 1 – 3.57 Year 2 – 1.00	\$ [redacted]	\$ [redacted]	\$ [redacted]
	QALYs			[redacted]	[redacted]	[redacted]
	Cost per QALY					\$ [redacted]
Average number of ranibizumab treatments	Costs	All patients Year 1 – 5.80 Year 2 – 1.00	[redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
	QALYs			[redacted]	[redacted]	[redacted]
	Cost per QALY					\$ [redacted]
Cost of blindness/month	Costs	Year 1 - [redacted] Subsequent years - [redacted]	\$0.00	\$ [redacted]	\$ [redacted]	\$ [redacted]
	QALYs			[redacted]	[redacted]	[redacted]
	Cost per QALY					\$ [redacted]

Rani = ranibizumab; Incr = incremental; AS = angiooid streaks; QALYs = quality-adjusted life years.

Note: An error was identified in the model where by the QALY gain for patients treated bilaterally was calculated by adding the QALY gain from the patients treated unilaterally in their WSE to those treated in their BSE. This has been corrected so that only the QALY gain for the BSE has been included.

Source: sensitivity analyses conducted during the evaluation, based on those presented in Table 3.9-1, p96, Section 3 of the submission, correcting for the error identified above and using EconomicModel\_Ranibizumab\_CNV.xlsx

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

6.49 The ESC also considered the frequency of injections and duration of therapy with ranibizumab to be highly uncertain, with the number of injections varying between the different aetiology subgroups. 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\*\* revealed that experience with ranibizumab in treating AMD in clinical practice showed the number of injections per patient 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

\*\* <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/aflibercept-ranibizumab-prd-2015-06>

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 average number of injections per patient was driving the overall cost-effectiveness (see Table 11 below). It should be noted that only the impact on costs has been assessed in the sensitivity analyses below.

**Table 11: Results of additional univariate and multivariate sensitivity analyses provided by the ESC**

#	Aspect	Base case value	Tested value or range		Rani	No active treatment	Incremental
	Base case (as per submission)	Costs			\$	\$	\$
		QALYs					
		Cost per QALY					\$
<b>Exploratory analyses</b>							
#	Aspect	Base case value	Tested value or range		Rani	No active treatment	Incremental
1	Relative risk of falls (consistent with PBAC base case in July 2014 ranibizumab submissions)	RR VA1 = 1 RR VA2 = 1 RR VA3 BSE = 1.55 RR VA3 WSE = 1 RR VA4 BSE = 1.55 RR VA4 WSE = 1	RR = 1	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
2	Monitoring Costs	Ranibizumab: 6, 4, and 1 visits in years 1, 2 and 3 respectively No active treatment: 8, 4, and 1 visits in years 1, 2 and 3 respectively	Set the number of monitoring costs to 1	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
3	Number of ranibizumab administrations	Year 1 – 5.80 Year 2 – 1.00	5.8 injections per year for the duration of the time horizon	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
4	#1 AND #3	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
5	#1 AND #2 AND #3	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
6	Number of ranibizumab administrations	Year 1 – 5.80 Year 2 – 1.00	Assume 8.4 administrations in year 1 and 7.1 administrations in year 2	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
7	#1 AND #6	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$

#	Aspect	Base case value	Tested value or range		Rani	No active treatment	Incremental
8	#1 AND #2 AND #6	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
9	Number of ranibizumab administrations	Year 1 – 5.80 Year 2 – 1.00	Assume 8.4 administrations in year 1 and 7.1 administrations in all subsequent years	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
10	#1 AND #9	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$
11	#1 AND #2 AND #9	As above	As above	Costs	\$	\$	\$
				QALYs			
				Cost per QALY			\$

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

Source: sensitivity analyses conducted during the evaluation, based on those presented in Table 3.9-1, p96, Section 3 of the submission, correcting for the error identified above and using EconomicModel\_Ranibizumab\_CNV.xlsx

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

6.50 These sensitivity analyses show that in addition to the frequency of injections, the model is also sensitive to the duration of therapy with ranibizumab. When 8.4 administrations in year 1 and 7.1 administrations in all subsequent years are applied to the model, the ICER increased to \$105,000/QALY - \$200,000/QALY.

6.51 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 rare CNV sourced from a literature search where the ICER ranged from less than \$15,000/QALY to \$15,000/QALY - \$45,000/QALY gained. The PBAC noted the data used to inform these alternative analysis were derived from studies including patients with CNV due to angioid streaks only and had not been evaluated.

**Drug cost/patient/year: \$**

6.52 The cost/patient/year was estimated to be \$. This was calculated assuming an average of 5.8 treatments per patient for unilateral treatment, as was observed over the 12 months following randomisation MINERVA, and a cost per treatment of \$. There was no robust data for the average number of ranibizumab injections beyond the first year.

**Estimated PBS usage & financial implications**

- 6.53 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 rare subfoveal CNV.
- 6.54 The submission stated that, as treatment for rare CNV is often completed within 12 months, only the incident population are relevant to estimates of patient numbers applicable to the proposed listing. The derivation of the incident population of rare CNV in the submission was extremely convoluted and involved estimating the prevalent population of patients with angioid streaks, the proportion of these patients who have CNV (referred to as the prevalent CNV/AS population in the submission), extrapolating this to estimate the 'total prevalent rare CNV population', and applying the estimated incidence of CNV due to angioid streaks to estimate the total incident population with rare CNV. The ESC considered the method used to estimate the prevalent patient population resulted in patient numbers that were highly uncertain, especially if the average duration of ranibizumab therapy is greater than 12 months.
- 6.55 Given the limited epidemiological data available for these rare causes of CNV, and the number of assumptions inherent in the method used to derive the eligible patient population, the estimated number of patients likely to be treated with ranibizumab under the requested restriction was highly uncertain. However, the ESC considered that the overall number of patients would still be small. As discussed above, there was also considerable uncertainty in the number of ranibizumab injections likely to be required per patient in the Australian clinical setting.
- 6.56 The submission assumed that PBS subsidised verteporfin and ranibizumab are currently being accessed for the treatment of rare CNV outside the PBS restriction for CNV due to AMD. The submission offset the estimated costs associated with this use of ranibizumab and verteporfin outside of their current restrictions. The submission's approach to include cost offsets for the prescribing of verteporfin and ranibizumab outside the PBS restrictions for CNV due to AMD is not appropriate. 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.

- 6.57 The derivation of the potential cost offsets resulting from displacement of current use of PBS listed medicines was based on the assumption that, in the current scenario, 20% of patients with rare CNV who are treated receive PBS subsidised VEGF inhibitor therapy and 2% of incident patients receive PBS-funded verteporfin. The remaining patients were assumed to be receiving treatment outside the PBS. The source of these assumptions was not clear.
- 6.58 The estimated use and financial implications to the PBS/RPBS and the MBS of listing ranibizumab for the treatment of CNV secondary to conditions other than AMD and PM are summarised in Table 12.

**Table 12: Estimated use and financial implications (effective prices)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of ranibizumab for rare CNV</b>						
Number of patients treated						
Number of scripts dispensed <sup>a</sup>						
<b>Estimated financial implications of ranibizumab for rare CNV</b>						
Cost to PBS/RPBS						
Co-payments				-\$14,807		
Cost to PBS/RPBS less co-payments						
<b>Estimated financial implications for current use of ranibizumab and verteporfin</b>						
Cost to PBS/RPBS						
Co-payments						
Cost to PBS/RPBS less co-payments						
<b>Net financial implications to the Australian government health budget</b>						
Net cost to PBS/RPBS						
<i>Cost without offsets due to use of PBS listed drugs outside the PBS restriction.</i>						
Net cost to MBS						
Net cost to PBS/RPBS/MBS						
<i>Cost without offsets due to use of PBS listed drugs outside the PBS restriction.</i>						

CNV = choroidal neovascularisation

<sup>a</sup> Assuming an average weighted 6.9 scripts per year across the angioid streaks and non-angioid streaks rare CNV subgroups, 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 4.2-3 p106, Table 4.3-5 p112, Table 4.3-6 p112 and Table 4.5-5 p120 of the submission; Excel workbook 'Utilisation and financial estimates Rare CNV.xlsx' supplied in the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10000, and the net cost to the PBS (without offsets due to use of PBS listed drugs outside the PBS restriction) would be less than \$10 million per year.

- 6.59 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.

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

- 6.60 The sponsor proposed that ranibizumab usage in rare CNV should be listed at the same published and effective prices as the AMD population and should be incorporated into the RSA negotiated to cover that population.
- 6.61 The proposal in the submission, which is restated in the PSCR, is to have the requested indication in rare CNV 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 rare CNV usage separate of AMD and RVO usage (such as separate PBS item numbers for each indication);
  - ways in which ranibizumab usage in rare CNV 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) due to rare causes (rare CNV). The PBAC was satisfied that ranibizumab provides, for some patients, a significant improvement in efficacy compared with sham injection (as a proxy for no active 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 rare CNV 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 of CNV (due to AMD, PM or rare causes – see also PSD Item 6.04 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 the nominated comparator of sham injection (as a proxy for no active treatment) was appropriate.

- 7.5 The PBAC noted that the submission was based on one head-to-head randomised trial, MINERVA, which compared ranibizumab treatment guided by disease activity with sham injection in patients with rare CNV. The PBAC noted that there was only 2 months of randomised comparative data available due to the majority of patients in the sham therapy arm switching to ranibizumab at the end of Month 2.
- 7.6 The PBAC noted that the mean difference in mean average change from baseline to Month 2 in best corrected visual acuity (BCVA) for ranibizumab over sham injection of 9.94 letters (95% CI: 6.97, 12.91), derived from 9.5 letters (95% CI: 6.97, 12.91) in the ranibizumab treatment arm compared to no change (-0.4 letters, 95% CI: -2.8, 1.9) in the sham injection arm. The PBAC considered the magnitude of treatment effect in the ranibizumab treatment arm over the first 2 months to be clinically meaningful also noting that  $\geq 40\%$  of patients in the ranibizumab treatment arm gained  $\geq 10$  letters or reached 84 letters at Month 2. The PBAC further noted that the CNV baseline aetiology subgroup analyses were indicative of a treatment benefit with ranibizumab for all causes of rare CNV, though the patient numbers were too small to accurately determine any true differences in treatment effect between each group. The PBAC recalled that it previously recommended extending the listing of ranibizumab to include treatment of diabetic macula 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. On the basis of evidence presented, the PBAC accepted the submission's proposed minimal clinically important difference of at least 5 letters, noting that mean BCVA in the MINERVA trial was at baseline was 62 letters.
- 7.7 The PBAC considered that, while the improvement in BCVA in the sham injection arm did not reach the same level of improvement as the ranibizumab arm after switching to ranibizumab at Month 2, this was not sufficient to support a benefit of earlier treatment given the substantial overlap in the CIs between the two arms (see Figure 2).
- 7.8 The PBAC therefore considered that the claim of superior efficacy over sham injection was reasonable.
- 7.9 The PBAC noted there was insufficient data to adequately evaluate the safety of ranibizumab compared with sham injection. 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.
- 7.10 The PBAC noted there was considerable variation in the number of ranibizumab injections across aetiology subgroups with CNV due to angioid streaks (AS) receiving a mean of ■■■ injections and CNV due to central serous chorioretinopathy (CSC) receiving an average of ■■■ injections. The PBAC noted that the submission stated that, based on expert opinion, a small number of patients will receive one additional

injection after the first year though no details on how this estimate was derived was provided. Further, the PBAC noted there is a lack of data for the distribution of underlying aetiologies among the rare CNV patients in Australian clinical practice. Taken together with the lack of long-term data beyond the 12 month duration of the trial, the PBAC considered there was some uncertainty in the average number of ranibizumab injections for the treatment of rare CNV which would be administered in clinical practice.

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

- The submission assumed that transition probabilities between visual acuity health states are the same for patients treated in the better or worse seeingeye or bilaterally.
- The transition probabilities for the sham injection arm were based on assumptions rather than changes in BCVA observed in the MINERVA trial or natural history data. The submission assumed patients would stay in the same health state as baseline in the first year.
- 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 MINERVA trial assuming a constant rate for both improving and worsening beyond Month 12.

However, the PBAC considered that the estimated transition probabilities 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.

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 double counting the cost of falls. The PBAC recalled that, at its July 2014 consideration of ranibizumab for the treatment of retinal vein occlusion (RVO) and DME, it had accepted a base case in both instances which did not include the cost of falls. However, the estimated consequences for falls had little effect on the ICER.

7.13 The PBAC noted the modelled analysis resulted in a base-case ICER of less than \$15,000 per QALY gained. The PBAC noted that the further sensitivity analyses provided by its ESC (see Table 11), 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 rare CNV, 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 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

\$105,000/QALY - \$200,000/QALY gained. The PBAC therefore considered that ranibizumab would not be cost-effective for the treatment of rare CNV 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  $\geq$ \$100,000 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.

- 7.14 The PBAC considered that the estimated number of prevalent patients was uncertain noting the limited available epidemiological data available for rare CNV. However, the PBAC considered that the number of patients was likely to be small overall and so the financial implications of listing would unlikely be substantial.
- 7.15 The PBAC considered that although it was possible that a proportion of patients with rare subfoveal CNV are currently receiving PBS-subsidised VEGF inhibitor therapy outside the PBS restriction 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 the PBS restriction) of substantially less than \$10 million per year in Year 6 was reasonable and there was a low risk of use outside the approved indication. 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]
- [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 secondary to pathologic myopia. 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	No. 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
1.65 mg/0.165 mL injection, 1 x 0.165 mL syringe				Pty. Ltd.	

<b>Condition:</b>	Subfoveal choroidal neovascularisation
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
<b>Clinical criteria:</b>	The condition must not be due to pathologic myopia  AND  The condition must not be due to age-related macular degeneration,  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.
<b>Prescriber Instructions</b>	Authority approval for initial treatment of each eye must be sought.  The first authority application for each eye must be made in writing or by telephone.  A written application must include:  a) a completed authority prescription form;  b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting

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	<p>Information Form; and</p> <p>c) a copy of the optical coherence tomography or fluorescein angiogram report.</p> <p>A telephone application must be made following submission by facsimile of a copy of a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.</p>
<b>Administrative Advice</b>	<p>The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p> <p>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.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. 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					

<b>Condition:</b>	Subfoveal choroidal neovascularisation
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.

<b>Clinical criteria:</b>	<p>The condition must not be due to pathologic myopia</p> <p>AND</p> <p>The condition must not be due to age-related macular degeneration,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye.</p>
<b>Administrative Advice</b>	<p>Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Special Pricing Arrangements apply.</p> <p>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.</p>

## 9 Context for Decision

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

## 10 Sponsor's Comment

The sponsor had no comment.