

6.01 AFLIBERCEPT,

Solution for intravitreal injection 4 mg in 100 microlitres (40 mg per mL) vial,

Solution for intravitreal injection 4 mg in 100 microlitres (40 mg per mL) pre-filled syringe,

Eylea[®],

Bayer Australia Ltd.

1 Purpose of Application

- 1.1 The submission requested an extension to the current Authority required PBS listing for aflibercept, to include treatment of visual impairment, caused by subfoveal choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) (hereafter referred to as mCNV). This is the first request for PBAC consideration of aflibercept for this population.
- 1.2 The submission was based on a cost-minimisation analysis (CMA) of aflibercept compared with ranibizumab in patients with mCNV. Both aflibercept and ranibizumab are anti-vascular endothelial growth factor (anti-VEGF) agents. The key components of the clinical issue addressed by the submission are summarised in Table 1.

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

Component	Description
Population	Patients with visual impairment due to subfoveal choroidal neovascularisation secondary to pathologic myopia (mCNV)
Intervention	Aflibercept 2.0 mg intraocular injection ^a
Comparator	Ranibizumab 0.5 mg intraocular injection ^a
Outcomes	Best corrected visual acuity (BCVA), quality of life ^b , safety
Clinical Claim	In patients with choroidal neovascularisation secondary to pathologic myopia, aflibercept is non-inferior in terms of efficacy and safety when compared to ranibizumab

^a Additional doses of aflibercept and ranibizumab are administered if there is evidence of disease activity. The interval between doses should not be shorter than one month for aflibercept and 4 weeks for ranibizumab (aflibercept and ranibizumab Product Information documents).

^b No quality of life data were presented in the main body of the submission.

Source: Table 1.1.1, p26 of the submission.

2 Requested listing

- 2.1 An abridged form of the sponsor's proposed listing is provided below. The Secretariat suggested the addition of administrative advice, and the deletion of the grandfathering restriction.

Public Summary Document – July 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
AFLIBERCEPT				Eylea® Bayer Australia Ltd
Single-use vial ^{a,b} 4 mg/0.1 mL, 1 x 0.1 mL	1	2	\$1,096.06 (published price) \$SPA ^c	
Pre-filled syringe ^{a,b} 4 mg/0.1 mL, 1 x 0.09 mL	1	2	\$1,096.06 (published price) \$SPA ^c	

SPA = special pricing arrangement.

^a Each vial and pre-filled syringe provides a usable amount to deliver a single dose of 50 µL solution for intravitreal injection containing 2.0 mg of aflibercept.

^b One vial is equivalent to one pre-filled syringe.

^c The submission stated that the sponsor was proposing price parity with the effective price for ranibizumab.

Source: Table 1.4.1, p34 of the submission.

Category / Program	Section 85 – General Schedule
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Subfoveal choroidal neovascularisation
Treatment phase	Initial treatment
Restriction	<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
Treatment criteria	Must be treated by an ophthalmologist or in consultation with an ophthalmologist
Clinical criteria	<u>Initial treatment</u> 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. <u>Continuing treatment</u> The condition must be due to pathologic myopia (PM), 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. <u>Grandfather treatment</u> The condition must be due to pathologic myopia (PM), AND Patients must have previously received non-PBS-subsidised treatment with this drug for this condition for the same eye prior to PBS listing, 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
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- 2.2 The submission proposed a special pricing arrangement (SPA), under which the effective price for one dose of aflibercept would be equal to the effective price of one dose of ranibizumab.
- 2.3 The requested listing was narrower than the TGA indication, which is for the treatment of visual impairment due to mCNV, irrespective of the location of the CNV. While the requested PBS restriction did not specify that patients must have visual impairment, it did limit eligibility to patients with subfoveal CNV, who would be expected to have some degree of visual impairment. Patients with visual impairment due to juxtafoveal or extrafoveal CNV lesions are not included in the restriction. The exclusion of juxtafoveal or extrafoveal CNV in the proposed listing is consistent with the PBS listing of ranibizumab. The ESC considered that limiting the listing of ranibizumab to subfoveal CNV secondary to PM would successfully target the group at highest risk of more extensive vision loss (paragraph 2.5, ranibizumab Public Summary Document (PSD), March 2018 PBAC Meeting). Only 60-70% of patients in the relevant treatment arms of the key trials presented in the submission had subfoveal CNV lesions.
- 2.4 The proposed treatment criteria and clinical criteria were consistent with those in the current listing for ranibizumab for subfoveal CNV due to PM.
- 2.5 Under the proposed restriction, patients who are intolerant or contraindicated to, or who have inadequate response on one anti-VEGF treatment, would be able to switch to the other. No clinical evidence was presented in the submission to support the use of aflibercept in patients who have previously failed treatment with ranibizumab, given that the trial populations were largely treatment naïve in the study eye.

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

3 Background

Registration status

- 3.1 Aflibercept was TGA registered on 24 February 2016 for the treatment of visual impairment due to mCNV.

Previous PBAC consideration

- 3.2 Aflibercept has not been previously considered by the PBAC for subfoveal mCNV. Aflibercept is currently PBS listed for diabetic macular oedema (DME), central retinal vein occlusion (CRVO) with macular oedema, and branch retinal vein occlusion with macular oedema (BRVO) and subfoveal CNV due to age-related macular degeneration (AMD). The ESC noted that the PBAC accepted the equivalence in efficacy and safety

between aflibercept and ranibizumab, and accepted a 1:1 dose relativity to ranibizumab in DME, CRVO, BRVO and AMD (aflibercept AMD PSD, March 2012 PBAC Meeting; paragraphs 7.10 and 7.12, aflibercept CRVO PSD, November 2014 PBAC Meeting; paragraph 7.11, aflibercept DME PSD, November 2014 PBAC Meeting; paragraph 7.8, aflibercept BRVO PSD, November 2015 PBAC Meeting).

- 3.3 Ranibizumab was considered by the PBAC for the same indication in March 2018, and subsequently listed on the PBS in November 2018 for the treatment of subfoveal CNV secondary to PM.

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.
- 4.2 Choroidal neovascularisation is classified according to location, based on the distance between the CNV and the fovea: subfoveal, juxtafoveal and extrafoveal. Subfoveal lesions are associated with worse visual outcomes when compared with juxtafoveal and extrafoveal subtypes. The submission requested listing of aflibercept for subfoveal mCNV.

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

5 Comparator

- 5.1 The submission nominated ranibizumab as the main comparator. The ESC considered this to be appropriate. The submission proposed that the availability of aflibercept would provide an alternative treatment option to ranibizumab for the same population while also allowing patients and clinicians an additional anti-VEGF therapy option for patients who are intolerant or contraindicated to, or who experience inadequate response on ranibizumab.

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 that no consumer comments were received for this item.

Clinical trials

- 6.3 No head-to-head trials were identified, and an adjusted indirect comparison was not possible, as there were no aflibercept and ranibizumab trials with common comparator arms. The submission was based on an informal indirect comparison of two randomised trials in patients with mCNV: one comparing intravitreal aflibercept with sham injection (MYRROR) (N=122), and the other one comparing two dosing regimens of intravitreal ranibizumab with verteporfin photodynamic therapy (vPDT) (RADIANCE) (N=277). RADIANCE was the key ranibizumab trial in the March 2018 ranibizumab submission to PBAC for the same population. The aflibercept submission presented an informal indirect comparison, in which the results from single arms from the trials were compared side-by-side, without performing any statistical analyses.
- 6.4 Prior to submission (September 2018), an on-line publication (ahead of print) of another trial comparing ranibizumab with vPDT (BRILLIANCE) became available, and relevant information was included during the evaluation. BRILLIANCE was also included in the March 2018 ranibizumab submission to the PBAC for treatment of subfoveal CNV secondary to PM, although at that time the trial had not been published. BRILLIANCE was identical in design to RADIANCE.
- 6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MYRROR	MYRROR CSR: A Phase-3, Multicentre, Randomised, Double-masked, Sham-controlled Study of the Efficacy, Safety, and Tolerability of Intravitreal VEGF Trap-Eye in Subjects with Choroidal Neovascularisation Secondary to Pathologic Myopia. Ikuno Y, Ohno-Matsui K, Wong T, et al. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularisation.	February 2014 <i>Ophthalmology</i> 2015;122(6):1220-1227
RADIANCE	Wolf S, Balciuniene V, Laganovska G, et al. RADIANCE: A Randomised Controlled Study of Ranibizumab in Patients with Choroidal Neovascularisation Secondary to Pathologic Myopia. Ceklic L, Munk M, Wolf-Schnurrbusch U, et al. Visual acuity outcomes of ranibizumab treatment in pathologic myopic eyes with macular retinoschisis and choroidal neovascularisation. Holz F, Tufail A, Leveziel N, Lai T, et al. Ranibizumab in Myopic Choroidal Neovascularisation: A Subgroup Analysis by Ethnicity, Age, and Ocular Characteristics in RADIANCE.	<i>Ophthalmology</i> 2014;121(3):682-692 <i>Retina</i> 2017;37(4):687-693 <i>Ophthalmologica</i> 2016;236(1):19-28
Additional trial identified during the evaluation		
BRILLIANCE	Chen Y, Sharma T, Li X, et al. Ranibizumab versus verteporfin photodynamic therapy in Asian patients with myopic choroidal neovascularization: BRILLIANCE, a 12-month, randomized, double-masked study.	<i>Retina</i> : published September 2018 ahead of print

CSR = Clinical Study Report

Source: Table 2.2.1, p44 of the submission

6.6 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence – informal indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Aflibercept vs. sham					
MYRROR	122	R, DB 48 weeks ^a	Low	mCNV	The change in BCVA in the study eye from baseline to Week 24
Ranibizumab vs. vPDT					
RADIANCE	277	R, DB 12 months ^b	Low	mCNV	Mean average BCVA change from baseline to month 1 through month 3 of the study eye
BRILLIANCE ^c	457	R, DB 12 months ^b	Low	mCNV	As above

BCVA = best correct visual acuity; DB = double blind; mCNV = choroidal neovascularisation secondary to pathologic myopia; R = randomised; vPDT = verteporfin photodynamic therapy.

^a As all patients randomised to sham injection were switched to intravitreal aflibercept at Week 24, only the first 24 weeks of the trial provide randomised comparative data for the efficacy and safety of aflibercept versus sham.

^b Duration of follow-up for the primary outcome, prior to the allowance of treatment switching for patients randomised to vPDT was 3 months.

^c Identified during the evaluation.

The total duration of follow-up in the trial was 12 months.

Source: compiled during the evaluation based on information presented in Section 2.2 to Section 2.4 of the submission, and Chen et al (2018).

6.7 The key features of the randomised trials are described in the text below.

Aflibercept trial: MYRROR

- Aflibercept – patients randomised to the aflibercept group received an intravitreal injection of aflibercept at baseline. Additional injections could be administered if CNV persisted or recurred (based on the assessment of predefined criteria for retreatment), at a maximum frequency of every 4 weeks, up to and including Week 44. If the patients did not meet the retreatment criteria, a sham injection was administered for masking purposes (N=91).
- Sham – patients randomised to the control group (sham) received sham injections every 4 weeks from baseline (Day 1) through Week 20. At Week 24, after assessment of the primary efficacy endpoint, sham patients received a mandatory intravitreal injection of aflibercept, followed by subsequent intravitreal aflibercept (if CNV persisted or recurred) or sham injection every 4 weeks to Week 44 (N=31).
- As all patients randomised to sham injection were switched to intravitreal aflibercept at Week 24, only the first 24 weeks of the trial provide randomised comparative data for the efficacy and safety of aflibercept versus sham.

Ranibizumab trial: RADIANCE

- Group I – Intravitreal ranibizumab 0.5 mg guided by visual acuity (VA) stabilisation criteria. Intravitreal ranibizumab was administered at baseline (Day 1) and at Month 1, and thereafter as needed guided by VA stabilisation criteria over the 12-month study period (N=106);
- Group II – Intravitreal ranibizumab 0.5 mg guided by disease activity criteria. Ranibizumab 0.5 mg was administered on Day 1, and thereafter as guided by disease activity criteria based on anatomical changes seen in fluorescein angiography (FA) or optical coherence tomography (OCT) (N=116);
- Group III – vPDT on Day 1. From Month 3, the investigator had the option to treat the patient's disease activity with intravitreal ranibizumab 0.5 mg, vPDT or both (N=55).

6.8 The submission used the results from Group II in RADIANCE in the indirect comparison, as clinician feedback suggested that the disease activity criteria used to guide retreatment in this arm were most consistent with the retreatment criteria applied in Australian clinical practice. This was reasonable.

6.9 Although the risk of bias was considered to be low for each of the individual trials, the risk of bias in the informal indirect comparison presented in the submission was high. In a comparison of treatment arms from separate studies, with no common reference arm, the confounding factors (both baseline prognostic factors and treatment effect modifiers) specific to each study are not controlled for. Furthermore, there is considerable potential for confounding from unmeasured factors and differences in study conduct and populations (transitivity issues).

6.10 In all the trials, only one eye was designated as the study eye. In patients who met the eligibility criteria in both eyes, the eye with the worst VA was selected as the study

eye. For the fellow eye, standard of care or other treatment for mCNV was allowed, as per the investigator's discretion. The outcomes of the trials were assessed in the study eye.

- 6.11 In contrast to RADIANCE, both MYRROR and BRILLIANCE were conducted in entirely Asian populations (mainly Japanese in MYRROR, and predominantly Chinese in BRILLIANCE). The submission claimed that this was not expected to have much impact on the efficacy and safety outcomes, as race has not been found to be a treatment effect modifier in mCNV, and hence the results of the MYRROR study are also relevant to non-Asian patients. In making this claim, the submission cited the March 2018 PSD for ranibizumab for mCNV, in which the PBAC noted that there was no evidence that race was a treatment effect modifier (paragraph 7.10, ranibizumab PSD, March 2018 PBAC Meeting). This statement was based on the fact that there was no clear evidence of treatment effect modification by race (Caucasian vs Asian) in RADIANCE (paragraph 6.8 of the PSD). As the pharmacological action of aflibercept and ranibizumab differ, the fact that race does not appear to modify the treatment effect of ranibizumab does not necessarily mean that this also applies to aflibercept. While this remains as a source of potential confounding in the informal indirect comparison, the TGA evaluator noted that the efficacy data for aflibercept for the indications of wet AMD, CRVO and DME, were comparable for Asian and Caucasian patients (Eylea TGA Clinical Evaluation Report, November 2015). The ESC considered that given race does not appear to modify the treatment effect of ranibizumab in mCNV and that the efficacy data for aflibercept were comparable for Asian and Caucasian patients in the indications of wet AMD, CRVO and DME, it was reasonable to assume that race was not a treatment effect modifier for use of aflibercept in mCNV.
- 6.12 The submission proposed a non-inferiority margin of ≤ 5 letters in best corrected visual acuity (BCVA) between aflibercept and ranibizumab, and stated that the PBAC had previously accepted a minimal clinically important difference (MCID) of ≥ 5 letters in its assessment of ranibizumab for mCNV. As stated in the ranibizumab PSD (paragraph 6.11, March 2018 PBAC meeting), the PBAC clarified that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye would 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.

Comparative effectiveness

- 6.13 The results of the primary outcome in MYRROR, change in BCVA from baseline to Week 24, are summarised in Table 4. The submission claimed that the results showed that aflibercept was clinically superior to sham. Given that the baseline mean BCVA in MYRROR was 56 letters, and that PBAC previously accepted a MCID of at least 5 letters in BCVA at a similar baseline BCVA in RADIANCE (55 letters), this claim was reasonable.

Table 4: Mean change in BCVA score from baseline at Week 24 (FASa, LOCF), MYRROR

	Aflibercept 2.0 mg ^b N = 90	Sham ^c N = 31
Mean baseline BCVA (letters), (SD)	56.4 (9.8)	56.6 (8.9)
Mean BCVA (letters) at Week 24, (SD)	68.5 (10.8)	54.6 (9.8)
Mean change (letters), (SD)	12.1 (8.3)	-2.0 (9.7)
Difference in LS means ^d , (95% CI)	14.1 (10.8, 17.4)	
p-value ^d	<0.0001	

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

^a FAS defined as all randomised patients who received any study drug and had a baseline and at least one-post-baseline BCVA assessment.

^b Aflibercept administered at baseline and potentially every 4 weeks in case of disease recurrence.

^c Sham injections administered at baseline and every 4 weeks through Week 20.

^d Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham) in LS mean changes, using an analysis of covariance (ANOVA) model with treatment group and country as fixed effects. Baseline value of BCVA was included in the model.

Note: BCVA was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at a distance of 4 metres.

Source: Table 2.5.1, p66 of the submission; p83, MYRROR 24 week CSR.

6.14 The results of the informal indirect comparison of aflibercept and ranibizumab for the treatment of mCNV are summarised in Table 5.

Table 5: Informal indirect comparison of effectiveness outcomes for aflibercept and ranibizumab for mCNV

Outcome	Aflibercept 2.0 mg	Ranibizumab 0.5 mg by disease activity (Group II)	
	MYRROR ^a N=90	RADIANCE ^b N=116	BRILLIANCE ^{b,e} N=184
Mean baseline BCVA (letters), (SD)	56.4 (9.8)	55.8 (12.6)	54.2 (13.0)
Mean average change in BCVA from baseline to Week 4/Month 1 through Week 12/Month 3 (SD) (95% CI) ^f	9.6 (6.8) ^c (8.2, 11.0)	10.6 (7.3) (9.3, 11.9)	9.8 (8.5) (8.6, 11.0)
Mean change from baseline over time (letters), (SD) (95% CI) ^f			
Week 12/Month 3	11.3 (7.6) (9.7, 12.9)	12.5 (8.8) (10.9, 14.1)	NR
Week 24/Month 6	12.1 (8.3) (10.4, 13.8)	12.7 (11.0) (10.7, 14.7)	NR
Week 48/Month 12	13.5 (8.8) (11.7, 15.3)	14.4 (10.2) (12.5, 16.3)	NR
Proportion of patients who achieved VA gain ≥ 15 letters, n (%)			
Week 12/Month 3	29 (32.2%)	50 (43.1%) ^d	59 (32.1%) ^d
Week 24/Month 6	35 (38.9%)	52 (44.8%) ^d	73 (39.7%) ^d
Week 48/Month 12	45 (50.0%)	60 (51.7%) ^d	75 (40.8%) ^d
Proportion of patients who achieved VA gain ≥ 10 letters, n (%)			
Week 12/Month 3	58 (64.4%)	76 (65.5%) ^d	107 (58.2%) ^d
Week 24/Month 6	57 (63.3%)	75 (64.7%) ^d	121 (65.8%) ^d
Week 48/Month 12	62 (68.9%)	80 (69.0%) ^d	115 (62.5%) ^d

mCNV = choroidal neovascularisation due to pathologic myopia; BCVA = best corrected visual acuity; NR = not reported; SD = standard deviation; VA = visual acuity.

^a FAS analysis, last observation carried forward (LOCF)

^b FAS analysis, modified LOCF

^c Post hoc analysis, performed for the submission.

^d Includes patient who reached 84 letters, regardless of their baseline BCVA

^e Added during the evaluation, based on data presented in Chen et al (2018)

^f 95% CIs calculated from mean and standard deviation values, and provided in Pre-Sub-Committee Response.

Note: BCVA was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at a distance of 4 metres.

Source: Table 2.6.1 p81, Table 2.6.14 p85, Table 2.6.15 p86, and Tables 2.6.16-19 pp88-89 of the submission; Table 3 p16, Table 6 p19 Ranibizumab European Public Assessment Report (Procedure No. EMEA/H/C/000715/II/0034); Table 1 p4, p5 and Figure 5 p7 Chen et al (2018); Table 1 Pre-Sub-Committee Response

- 6.15 The submission stated that the mean change from baseline in BCVA measured at Week 24 was the primary outcome in MYRROR and was also assessed in RADIANCE, and was the most appropriate time point to compare between the trials. The mean change from baseline in BCVA measured at Week 24 with aflibercept was 12.1 letters (standard deviation (SD) 8.3) compared to 12.7 (SD 11.0) letters at Month 6 with ranibizumab. The submission stated that this difference was within the margin of non-inferiority of ≤ 5 letters, supporting the claim that aflibercept was non-inferior in terms of effectiveness compared with ranibizumab. Similarly, it also stated that the difference between aflibercept and ranibizumab for the outcome of mean average change in BCVA from baseline to Week 4/Month 1 through Week 12/Month 3 (-1 letter) was also within the margin of non-inferiority. The fact that the point estimate of the difference in the outcomes between the treatment arms lies within the non-inferiority margin is not sufficient to support a claim of non-inferiority. In order to demonstrate non-inferiority, the lower boundary of the 95% confidence interval (CI) for the comparative treatment effect must be within the predefined non-inferiority margin.
- 6.16 The Pre-Sub-Committee Response (PSCR) provided the 95% CIs for the outcome of mean average change in BCVA from baseline to Week 4/Month 1 through Week 12/Month 3 and mean change in baseline over time (letters) for the informal indirect comparison of aflibercept and ranibizumab (see Table 5 above). In addition, the PSCR provided the results of independent samples t-tests comparing the outcomes for aflibercept and ranibizumab (Table 6).

Table 6: Independent samples t-test results for the informal indirect comparison of effectiveness outcomes for aflibercept and ranibizumab for mCNV

Outcome	Aflibercept 2.0 mg	Ranibizumab 0.5 mg by disease activity (Group II)	
	MYRROR ^a N=90	RADIANCE ^b N=116	BRILLIANCE ^b N=184
Mean average change in BCVA from baseline to Week 4/Month 1 through Week 12/Month 3, (ETDRS letters), (95% CI)	9.6 (8.2, 11.0)	10.6 (9.3, 11.9)	9.8 (8.6, 11.0)
Estimated difference, ETDRS letters (95% CI) (aflibercept – ranibizumab)	N/a	-1 (-2.96, 0.96); p=0.32	-0.2 (-2.36, 1.96); p=0.86*
Estimated difference, mean ETDRS letters (95% CI), p-value at:			
Week 12/Month 3 (aflibercept – ranibizumab)	N/a	-1.20 (-3.50, 1.10); p=0.30	NR
Week 24/Month 6 (aflibercept – ranibizumab)	N/a	-0.60 (-3.34, 2.15); p=0.67	NR
Week 48/Month 12 (aflibercept – ranibizumab)	N/a	-0.90 (-3.56, 1.76); p=0.51	NR

Abbreviations: BCVA, Best Corrected Visual Acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; N/a, not applicable; NR, not reported

^a FAS analysis, last observation carried forward (LOCF)

^b FAS analysis, modified LOCF

* Noted during preparation of ESC Advice that using STATA ttesti command this is -0.20 (95% CI: -2.22, 1.82)

Note: BCVA was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at a distance of 4 metres.

Source: Pre-Sub-Committee Response, p2.

- 6.17 The PSCR noted that at Week 12/Month 3, the mean difference was -1.20 letters (95% CI -3.50, 1.10), at Week 24/Month 6, the mean difference was -0.60 letters (95% CI -3.34, 2.15) and at Week 48/Month 12 -0.90 letters (95% CI -3.56, 1.76) (Table 6). The PSCR argued that the results showed that the treatment effect of aflibercept compared to ranibizumab was not statistically significantly different, and that the lower bound estimates of the 95% CIs fell within the MCID and non-inferiority margin of 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters.
- 6.18 The ESC considered that these results were difficult to interpret. The ESC noted that as with all informal indirect comparisons, the results of the single treatment arms from the two studies are compared as if they were from a single trial and the indirectly derived CI does not take into account between study variations. Therefore, the resulting CIs underestimate the true extent of statistical uncertainty in the synthesised estimate of the comparative treatment effect*. Furthermore, in an unadjusted indirect comparison, it is not possible to use the event rate in a common reference arm to assess and adjust for any imbalances in both observed and unobserved confounding factors that may exist.
- 6.19 The ESC considered that the similarity in the point estimates reported for aflibercept and ranibizumab for the outcomes of mean change from baseline in BCVA measured at Week 24 along with the supplementary statistical analysis provided in the PSCR provided reassurance of therapeutic equivalence, but alone do not mitigate the concern regarding the uncertainty of the claim of non-inferior efficacy.
- 6.20 The submission claimed that, in clinical practice, retreatment with aflibercept will be based on the same criteria as those used for retreatment with ranibizumab, and that, as the minimum dosing interval was the same for both drugs, patients are likely to receive the same number of injections of both drugs in clinical practice, despite the minor differences in the average number of injections seen in the MYRROR and Group II of the RADIANCE trials (mean: 4.2 over 48 weeks, and 3.5 over 12 months respectively, see Table 9 below). The submission noted that the retreatment criteria for aflibercept in MYRROR were less stringent than those for ranibizumab in RADIANCE (Group II), with the latter criteria more likely to reflect those used in clinical practice. If the retreatment criteria used in MYRROR were less stringent than those applied in Australian clinical practice, then the outcomes of MYRROR may overestimate the outcomes that would be achieved in clinical practice. The PSCR argued that when aflibercept and ranibizumab are used according to the same PBS restriction criteria for the treatment of mCNV, it is reasonable to assume that the number of injections per patient will be identical with similar outcomes based on relative utilisation seen in AMD, DME, BRVO and CRVO in Australian practice. Furthermore, it argued that the

* Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee. Report of the Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee assessing indirect comparisons. 2009.

PBAC has previously accepted the equivalence in efficacy and safety between aflibercept and ranibizumab and accepted a 1:1 dose relativity to ranibizumab for these indications. The ESC considered it unlikely that clinicians would differ in their use of ranibizumab and aflibercept for mCNV. In addition, the ESC noted that in Group I of RADIANCE (guided by visual acuity (VA) stabilisation criteria), the mean number of injections was 4.6 in 12 months. Thus, it considered it was not unreasonable to assume that differences in the mean number of injections between Group II of RADIANCE and MYRROR were most likely due to the re-treatment criteria in these trials.

Comparative harms

6.21 A comparison of adverse events (AEs) in the aflibercept arm of MYRROR with those observed in Group II of RADIANCE and BRILLIANCE is presented in Table 7.

Table 7: Comparison of adverse events in the aflibercept treatment arm of MYRROR and Group II of RADIANCE and BRILLIANCE (SAF).

	Aflibercept 2.0 mg N=91	Ranibizumab 0.5 mg Group II; guided by disease activity	
		RADIANCE N=118	BRILLIANCE ^a N=185
Duration of follow-up	48 weeks	12 months	12 months
Exposure, no. Injections (SD)	4.2 (3.1)	3.5 (3.0)	3.9 (2.5)
Adverse events	n (%)	n (%)	n (%)
Discontinuation due to AE	4 (4.4)	1 (0.8)	1 (0.5)
Serious ocular AEs in study eye			
In the study eye	1 (1.1)	1 (0.8)	1 (0.5)
In the fellow eye	2 (2.2)	0 (0.0)	NR
Serious non-ocular AEs	4 (4.4)	5 (4.2)	13 (7.0)
Ocular AEs total	29 (31.9)	44 (37.3)	55 (29.7)
Conjunctival haemorrhage	10 (11.0)	12 (10.2)	14 (7.6)
Dry Eye	7 (7.7)	2 (1.7)	7 (3.8)
Eye pain	7 (7.7)	4 (3.4)	5 (2.7)
Punctate keratitis	6 (6.6)	3 (2.5)	NR
Non-ocular AEs	53 (58.2)	51 (43.2)	94 (50.8)
Nasopharyngitis	17 (18.7)	12 (10.2)	20 (10.8)
Headache	6 (6.6)	11 (9.3)	NR

AEs = adverse events; NR = not reported; SAF = safety analysis set; SD = standard deviation.

^a Added during the evaluation, based on data presented in Chen et al (2018).

Source: Tables 2.6.12 and 2.6.13 p84 and Table 2.6.23 p92 of the submission; Wolf et al (2014); Chen et al (2018).

6.22 The submission claimed that, overall, the safety profile for aflibercept was similar to that of ranibizumab, with no AEs or serious AEs that were substantially higher in patients treated with one treatment compared to the other. The submission concluded that aflibercept can be considered non-inferior to ranibizumab in terms of safety in patients with mCNV. Given the differences in classification of AEs across the trials, and the fact that there is a degree of subjectivity in grading of the severity of AEs, comparisons of these results across the trials should be interpreted with caution.

Clinical claim

- 6.23 The submission described aflibercept as non-inferior to ranibizumab in terms of both efficacy and safety in patients with visual impairment due to subfoveal CNV secondary to pathologic myopia.
- 6.24 The therapeutic conclusion of non-inferior effectiveness of aflibercept compared to ranibizumab was not comprehensively supported by the evidence presented in the submission, due to the unadjusted, indirect nature of the comparison and the lack of statistical estimates of the 95% CIs for any of the comparative treatment effects. The PSCR provided the 95% CIs for key comparative treatment effects and independent samples t-tests comparing outcomes for aflibercept and ranibizumab. The ESC noted that aflibercept and ranibizumab are both anti-VEGF agents and that the PBAC has previously accepted evidence of their equi-effectiveness in other related eye disorders (AMD, CRVO, BRVO and DME). The ESC acknowledged the uncertainty associated with the informal indirect comparison, noted the point estimate equivalency and the supplementary statistical analysis presented in PSCR, and considered that the weight of evidence could reasonably be considered to support a claim of non-inferiority.
- 6.25 Although the non-inferior safety of aflibercept compared to ranibizumab was also not comprehensively supported by the evidence presented, the overall safety profiles of both aflibercept and ranibizumab for the treatment of mCNV were consistent with the known safety profiles of each of these drugs for treatment of other ocular indications for which they have been approved (Eylea Clinical Evaluation Report, November 2015; TGA Australian Public Assessment Report for Ranibizumab[†]). The ESC considered that the evidence presented in the submission does not suggest a difference in safety profiles between aflibercept and ranibizumab.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.27 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.28 The submission presented a CMA of aflibercept 2.0 mg intravitreal injection compared to ranibizumab 0.5 mg intravitreal injection, based on a non-inferiority claim. This is only appropriate if the submission's claim that aflibercept is non-inferior to ranibizumab, in terms of both effectiveness and safety, is accepted.
- 6.29 The submission proposed price parity between the effective price of aflibercept and the effective price of ranibizumab for this indication. The approved published ex-

[†] Available at: <https://www.tga.gov.au/auspar/auspar-ranibizumab-1>

manufacturer price (AEMP) for aflibercept (\$984.20), equating to a dispensed price maximum quantity (DPMQ) of \$1,096.06, was used as a proxy to show effective price parity.

- 6.30 The submission stated that, the average number of injections per patient was likely to be the same on either aflibercept or ranibizumab treatment, as patients would be monitored and re-treated using the same criteria. The submission further noted that, in consideration of aflibercept for other ocular conditions, the PBAC accepted the equivalence in efficacy and safety between aflibercept and ranibizumab, and accepted a 1:1 dose relativity (price parity) to ranibizumab (aflibercept AMD PSD, March 2012 PBAC Meeting; paragraphs 7.10 and 7.12, aflibercept CRVO PSD, November 2014 PBAC Meeting; paragraph 7.11, aflibercept DME PSD, November 2014 PBAC Meeting; paragraph 7.8, aflibercept BRVO PSD, November 2015 PBAC Meeting).
- 6.31 On this basis, the submission assumed that aflibercept 2.0 mg 3.5 injections per patient was equi-effective to ranibizumab 0.5 mg 3.5 injections per patient over the first year of treatment in mCNV.
- 6.32 The number of injections administered in the aflibercept treatment group in MYRROR from baseline to Week 48, and in Group II (ranibizumab guided by disease activity) in RADIANCE and BRILLIANCE from baseline to Month 12, are summarised in Table 8.

Table 8: Treatment exposure (number of injections) from baseline to Week 48 in MYRROR, and from baseline to Month 12 in RADIANCE and BRILLIANCE

	Aflibercept 2.0 mg	Ranibizumab 0.5 mg by disease activity (Group II)	
	MYRROR ^a N=90	RADIANCE ^a N=116	BRILLIANCE ^b N=185
Duration of follow-up	48 weeks	12 months	
Number of injections per patient			
Mean (SD)	4.2 (3.1) ^c	3.5 (3.0)	3.9 (2.5)
Median (range)	3.0 (1-12)	2.0 (NR)	3.0 (NR)

NR = not reported; SD = standard deviation.

^a Full analysis set

^b Safety set, figures added during the evaluation, based on data presented in Chen et al (2018).

^c For the subfoveal subgroup in MYRROR, the mean number of injections per patient was 4.0 (SD 2.8). The frequency of injection in this subgroup was similar to that for the FAS (Table 2.6.11, p83 of the submission).

Source: Tables 2.6.11, 2.6.22, p83, 91 of the submission; Table 2 Chen et al (2018)

- 6.33 The submission acknowledged that the mean number of injections per patient was higher in the aflibercept treatment group in MYRROR (mean: 4.2 over 48 weeks) compared with the ranibizumab treatment Group II in RADIANCE (mean: 3.5 over 12 months). The submission proposed that this disparity may be attributable to the differences in retreatment criteria between the two trials. As discussed above, if the retreatment criteria and, consequently, the mean number of injections per patient used in MYRROR differed from Australian clinical practice, then the outcomes of the trial are also likely to differ from those that would be observed in clinical practice. However, it is also possible that the difference in the average number of injections per patient in MYRROR and RADIANCE may have been due to some unidentified difference

between the two trial populations. The PBAC agreed with the ESC that the differences in the mean number of injections between Group II of RADIANCE and MYRROR were most likely due to the re-treatment criteria in these trials. The PBAC considered it unlikely that clinicians would differ in their use of ranibizumab and aflibercept in mCNV.

- 6.34 The results of the CMA are presented in Table 9. The ESC noted that the evaluation had presented a sensitivity analysis based on the number of injections per patient used to obtain the clinical outcomes on which the non-inferiority claim was made in the base case of the CMA, i.e. an average of 4.2 injections of aflibercept and 3.5 injections of ranibizumab over the first year of treatment. The ESC advised that 1:1 dose relativity was not an unreasonable assumption given considerations discussed above (paragraph 6.20), and also evidence from a recent DUSC analysis which reported that, for AMD, DME and retinal vein occlusion (RVO), the number of injections in a patient’s first year of treatment were nearly identical for patients solely treated with either ranibizumab or aflibercept, consistent with the PBAC’s consideration that these medicines should be priced on an injection:injection basis (Ranibizumab and aflibercept: analysis of use for AMD, DME, BRVO and CRVO, Public Release Document, May 2018 DUSC Meeting).

Table 9: Results of the cost minimisation analysis, using a proxy effective price for ranibizumab.

		Aflibercept		Ranibizumab
		Base case	Sensitivity analysis ^a	
A	Mean number of injections	3.5	4.2	3.5
B	Drug cost	\$1,096.06	\$863.26	\$1,096.06 ^b
C=AxB	Total drug cost	\$3,836.21	\$3,625.69	\$3,836.21
D	Total cost of diagnosis (OCT)	\$40.00	\$40.00	\$40.00
E	Drug administration cost	\$300.75	\$300.75	\$300.75
F=AxE	Total drug administration cost	\$1,052.63	\$1,263.15	\$1,052.63
G=C+D+F	Total cost (based on current aflibercept DPMQ)	\$4,928.84	\$4,928.84	\$4,928.84

DPMQ = dispensed price maximum quantity; OCT = optical coherence tomography.

^a Sensitivity analysis performed during the evaluation, assuming patients receive an average of 4.2 injection of aflibercept over the first year of treatment.

^b Based on proxy effective DPMQ (i.e. the published DPMQ for aflibercept)

Source: Table 3.3.1, p99 of the submission.

- 6.35 All costs relating to safety and toxicity management were assumed to be equal for both drugs, and were not included in the CMA. This was reasonable.

Drug cost/patient/course

- 6.36 The total drug cost of aflibercept per patient over the first year of treatment would be \$3,836, based on the current published DPMQ for aflibercept (\$1,096.06), and assuming 3.5 injections per patient over 12 months, as observed for ranibizumab in the ranibizumab trial (RADIANCE) (Table 10). The submission proposed price parity to match the effective price of aflibercept to the effective price of ranibizumab. The PBAC noted that the drug cost per patient for aflibercept would need to be updated based

on the effective price of ranibizumab.

Table 10: Drug cost per patient for aflibercept and ranibizumab for mCNV

	Aflibercept			Ranibizumab		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
Dose	2.0 mg ^a	2.0 mg ^a	2.0 mg ^a	0.5 mg ^b	0.5 mg ^b	0.5 mg ^b
Mean injections per patient	4.2 over 48 weeks	3.5 ^c over 12 months	5.5 ^d	3.5 over 12 months	3.5 over 12 months	5.5 ^d
Cost/injection	\$1,096.06 ^e	\$1,096.06 ^e	\$1,096.06 ^e	\$1,096.06 ^e	\$1,096.06 ^e	\$1,096.06 ^e
Cost/patient/course	\$4,603.45 ^f	\$3,836.21	\$6,028.33 ^f	\$3,836.21	\$3,836.21	\$6,028.33 ^f

CMA = cost-minimisation analysis; mCNV = choroidal neovascularisation secondary to pathologic myopia

^a Administered as a single intravitreal injection, at a minimum interval of 4 weeks.

^b Administered as a single intravitreal injection, at a minimum interval of 1 month.

^c The submission assumed that, in clinical practice, the mean number of injections per patient for aflibercept over the first year of treatment would be the same as the mean number of injections of ranibizumab in Group II of the RADIANCE trial, on the basis that the retreatment criteria for ranibizumab in Group II were most consistent with those that would be applied in the Australian clinical setting.

^d This assumed that a proportion of patients receive an addition injection after the first year of treatment, and that some patients require bilateral treatment.

^e The current published DPMQ for aflibercept was used as a proxy for the effective price of ranibizumab.

^f Calculated during the evaluation (mean injections per patient x \$1,096.06).

Source: Table 1.1.1 p26, Table 3.1.1 p97, Table 3.2.1 p98, and Table 4.1.1 p103 of the submission.

Estimated PBS usage & financial implications

- 6.37 This submission was not considered by DUSC. The submission used a combined epidemiological and market share approach to estimate the usage and financial impact associated with the proposed listing of aflibercept for the treatment of subfoveal mCNV. The estimation of the eligible population and the likely number of injections per patient were derived using the same approach and similar assumptions as those used in the March 2018 submission for ranibizumab for mCNV (ranibizumab PSD, March 2018 PBAC Meeting).
- 6.38 Consistent with the equi-effective doses nominated in the CMA, the submission assumed that one injection of aflibercept substitutes for one injection of ranibizumab, and that patients would receive the same number of injections with both drugs.
- 6.39 At the time of evaluation, there were only limited PBS statistics available for ranibizumab for the treatment of mCNV, as it was listed on 1 November 2018 – there were only 74 services for both mCNV and CNV not due to PM or AMD[‡] in each of January and February 2019. Given that clinicians are already familiar with using intravitreal anti-VEGF for ocular indications, these figures suggested that the submission’s estimate of the number of scripts for aflibercept (3,651 in Year 1, increasing to approximately 4,000 in Year 6) may have been an overestimate.

[‡] PBS items 11480F and 11471R

6.40 The estimated use and financial implications to the PBS/RPBS of listing aflibercept for the treatment of mCNV are summarised in Table 11.

Table 11: Estimate use and financial implications*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients likely to be treated						
Cost to PBS/RPBS for aflibercept for the requested restriction						
Total scripts dispensed						
Cost to PBS/RPBS						
Less patient co-payment						
Net cost to PBS/RPBS						
Cost offsets from displacement of ranibizumab						
Reduction in scripts						
Savings to PBS/RPBS						
Less patient co-payments						
Net cost offsets PBS/RPBS						
Net financial implications for the PBS/RPBS						
Net financial implications						

* Using the current published DPMQ of aflibercept of \$1,096.06 as a proxy effective price for ranibizumab.
 Source: Table 4.4.1 p105, and Table 4.2.3 p110 of the submission; Excel workbook 4A, Eylea_PM_BudgetImpact.xlsx.
 NB: Minor discrepancies in figures (net impact of -\$14 over six years) were identified during the evaluation.

The redacted table shows that the estimated number of patients and scripts over 6 years was less than 10,000 and the net cost for the PBS was less than \$10 million.

6.41 The main sources of uncertainty in the financial estimates were the size of the eligible population, and the average number of injections of both aflibercept and ranibizumab required per patient.

6.42 The submission stated that the listing of aflibercept was not expected to result in expansion of the mCNV market or leakage to other indications. There is the possibility that patients who have poor response to one anti-VEGF agent may be switched to the alternative drug. In addition, it is possible that aflibercept will be used in a small number of patients who are intolerant to ranibizumab, and vice versa; however, given the relatively good safety profile of both anti-VEGF agents, this is likely to be minimal.

6.43 The submission stated that as the requirements for diagnosis of mCNV would not be altered by the listing of aflibercept, and as the utilisation of both ranibizumab and aflibercept (in terms of number of injections per patient) was expected to be identical, with no market growth, there was not expected to be any change in the use of MBS items.

Financial Management – Risk Sharing Arrangements

6.44 The submission stated that the sponsor is willing to work with the Department to ensure that there was an equivalent Commonwealth cost for aflibercept when compared to ranibizumab in mCNV.

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

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of aflibercept as an Authority required benefit to include treatment of subfoveal choroidal neovascularisation secondary to pathologic myopia (mCNV).
- 7.2 The PBAC recommended the listing of aflibercept on a cost-minimisation basis with ranibizumab. The PBAC recommended that the equi-effective doses for mCNV were aflibercept 2 mg injection and ranibizumab 0.5 mg injection.
- 7.3 The PBAC noted that the submission was based on an informal indirect comparison between the MYRROR and RADIANCE trials. The PBAC noted that, in contrast to the RADIANCE trial, the MYRROR trial was conducted in an entirely Asian population. However, the PBAC agreed with the ESC's assessment that it was reasonable to assume that race was not a treatment effect modifier for the use of aflibercept in mCNV.
- 7.4 The PBAC agreed with the ESC that there was uncertainty associated with the informal indirect comparison, but that the point estimate equivalency and supplementary statistical analysis presented in PSCR were supportive of the non-inferiority claim. Moreover, the PBAC recalled that it had previously accepted the equivalence in efficacy and safety between aflibercept and ranibizumab in subfoveal CNV due to AMD. The PBAC recalled that this previous recommendation was based on two direct randomised controlled trials and one pre-specified pooled analysis of two trials comparing aflibercept with ranibizumab in patients with AMD (aflibercept AMD PSD, March 2012 PBAC Meeting). Given the strength of this previous evidence, and noting that CNV has similar consequences regardless of origin (and so there was nothing to suggest the comparative effect between the drugs would be different across the two indications), the PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 7.5 The PBAC agreed with the ESC that the evidence presented in the submission did not suggest a difference in safety profiles between aflibercept and ranibizumab, and considered that a claim of non-inferior comparative safety was reasonable.
- 7.6 The PBAC recalled that it had previously accepted 1:1 dose relatively to ranibizumab in patients with AMD (aflibercept AMD PSD, March 2012 PBAC Meeting). The PBAC noted that the cost-minimisation analysis presented assumed 1:1 dose relativity, but that the mean number of injections per patient was higher in the aflibercept treatment group in MYRROR compared with the ranibizumab treatment Group II in RADIANCE (4.2 over 48 weeks and 3.5 over 12 months respectively). However, the PBAC agreed with the ESC that it is unlikely that clinicians would differ in their use of ranibizumab and aflibercept for mCNV and that the differences in the mean number of injections reported was most likely due to the re-treatment criteria in these trials. The PBAC also noted that the May 2018 DUSC analysis of ranibizumab and aflibercept reported the number of injections per patient in the first year of treatment to be

nearly identical when used in AMD, DME and RVO and considered this supportive of the assumption of 1:1 dose relativity.

- 7.7 The PBAC noted the financial estimates presented in the submission and the PBS statistics available for ranibizumab for the treatment of mCNV.
- 7.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because aflibercept is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ranibizumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.9 The PBAC recommended that aflibercept should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.10 The PBAC noted that submission requested listing for both a vial and pre-filled syringe presentation. The PBAC noted that the pre-filled syringe is not currently marketed in Australia, and that it had previously recommended that the presentations be ‘a’ flagged on the PBS for AMD, CRVO and DME (6.08 aflibercept PSD, March 2015 PBAC Meeting). The PBAC advised, under Section 101 (4AACD) of the *National Health Act*, that aflibercept, 4 mg/0.1 mL injection, 0.1 mL syringe and aflibercept, 4 mg/0.1 mL injection, 0.1 mL vial should be considered equivalent for the purposes of substitution (i.e., ‘a’ flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution).
- 7.11 The PBAC advised that aflibercept is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC recommended that the PBS listing for aflibercept for mCNV should be the same Authority levels and wording as ranibizumab for the initial and continuing phase (that is, Authority required in writing for initiation and telephone Authority for continuation). The PBAC considered that a grandfathering restriction was not needed as patients would be able to access treatment via the initial phase listing, which has the same criteria. The PBAC also recommended the removal of the existing ranibizumab grandfathering restriction for CNV. The PBAC noted that the existing Department of Human Services’ initial PBS authority application form for subfoveal CNV will need to be updated.
- 7.14 In addition, the PBAC recommended amending existing notes for the following indications to clarify that no increase in the maximum quantity or number of units may be authorised for the treatment of 1 eye. However, for the treatment of 2 eyes at the same time, an increase in maximum quantity or units of up to 2 will be authorised.
- Aflibercept for DME, BRVO, CRVO
 - Ranibizumab for DME, BRVO, CRVO and CNV due to AMD
 - Dexamethasone implant for BRVO and CRVO

- 7.15 The PBAC also noted that existing listings for aflibercept for CNV due to AMD, and ranibizumab for mCNV and “rare CNV” do not currently have notes preventing increases to the maximum quantities and number of units. For consistency, the PBAC recommended that these be added as per amendments in the paragraph above, and that the same note also apply to the new listing for aflibercept for mCNV.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
AFLIBERCEPT 4 mg/0.1 mL injection, 0.1 mL syringe 4 mg/0.1 mL injection, 0.1 mL vial	1	2	Eylea®	Bayer Australia Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Subfoveal choroidal neovascularisation
PBS Indication:	Subfoveal choroidal neovascularisation
Treatment phase:	Initial treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic
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.

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Administrative Advice:	<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 www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.</p> <p>Where both eyes are being treated simultaneously, a quantity of 2 vials can be requested on the same authority prescription form.</p>
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Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Subfoveal choroidal neovascularisation
PBS Indication:	Subfoveal choroidal neovascularisation
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – Telephone/Electronic
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 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:	<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>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.</p> <p>Where both eyes are being treated simultaneously, a quantity of 2 vials can be requested on the same authority prescription form.</p>

8.2 Flow on changes: amendments and additions of administrative notes as follows.

“No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.

Where both eyes are being treated simultaneously, a quantity of 2 vials can be requested on the same authority prescription form.”

To be applied to the following items:

- Aflibercept 10505X, 2168D
- Ranibizumab 10138N, 10373Y, 10374B, 11471R, 11480F, 1382R
- Dexamethasone implant 11469P

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

Bayer welcomes the PBAC decision to recommend the PBS listing of Eylea for the treatment of subfoveal choroidal neovascularisation secondary to pathologic myopia (mCNV).