

**5.03 AFLIBERCEPT,
Solution for intravitreal injection,
11.43 mg in 100 microlitres (114.3 mg per mL)
pre-filled syringe,
Eylea[®],
Bayer Australia Limited**

1 Purpose of submission

- 1.1 The Category 2 submission requested Section 85 Authority Required listing for aflibercept 8 mg pre-filled syringe (PFS) for the treatment of sub-foveal choroidal neovascularisation (CNV) secondary to age-related macular degeneration (AMD) (neovascular age-related macular degeneration (nAMD)).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus aflibercept 2 mg.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with visual impairment due to sub-foveal choroidal neovascularisation secondary to age-related macular degeneration (AMD)
Intervention	Aflibercept 8.0 mg intravitreal injection (pre-filled syringe)
Comparator	Aflibercept 2.0 mg intravitreal injection
Outcomes	Best corrected visual acuity (BCVA), quality of life, safety
Clinical claim	In patients with sub-foveal choroidal neovascularisation due to AMD, aflibercept 8.0 mg is non-inferior in terms of efficacy and safety when compared to aflibercept 2.0 mg

Source: Table 1.2, p5 of the submission.

- 1.3 A submission for aflibercept 8 mg PFS for the treatment of diabetic macular oedema (DMO) was also considered at the November 2024 Pharmaceutical Benefits Advisory Committee (PBAC) meeting.

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration aflibercept 8 mg pre-filled syringe was registered on the Australian Register of Therapeutic Goods.
- 2.2 The submission stated that an application to update the Product Information (PI) to allow extension of dosing intervals up to 20 weeks had been submitted to the TGA with approval expected. No TGA planning letter was provided with the submission and it is unclear if the submission had been lodged with the TGA at the time of submitting to PBAC.

Previous PBAC consideration

- 2.3 The PBAC recommended listing of aflibercept in an 8 mg vial presentation at the May 2024 intracycle meeting for both nAMD and diabetic macular oedema (DMO). Aflibercept 8 mg vial was listed on the PBS in October 2024. The submission, for both the 8 mg vial and the 8 mg PFS dosage forms, was originally submitted for the March meeting 2024 but was held over until the May 2024 intracycle-meeting. The PFS was not considered at the meeting as it had not yet been submitted to the TGA for approval (Paragraph 3.2, Aflibercept Public Summary Document (PSD), May 2024 PBAC meeting).
- 2.4 The PBAC previously noted that:
- the cost-effectiveness of aflibercept 8 mg would be acceptable if it were cost-minimised to the lowest cost PBS-listed anti-VEGF treatment for the same indication (Paragraph 7.8, Aflibercept nAMD PSD, May 2024 PBAC Meeting);
 - the nominated comparator of aflibercept 2 mg was appropriate, and aflibercept 2 mg, faricimab and ranibizumab were all alternative therapies as they could be replaced in clinical practice, and no evidence was provided to demonstrate aflibercept 8 mg provided a significant improvement in efficacy and/or reduction of toxicity over the alternative therapies (Paragraph 7.4, Aflibercept nAMD PSD, May 2024 PBAC Meeting);
 - the equi-effective doses proposed by the sponsor favoured aflibercept, and the equi-effective doses used in the CMA should be those previously accepted for faricimab:
 - Year 1: 7.20 injections of aflibercept 8 mg/faricimab to 7.69 injections of aflibercept 2 mg/ranibizumab
 - Year 2: 4.30 injections of aflibercept 8 mg/faricimab to 6.31 injections of aflibercept 2 mg/ranibizumab (Paragraph 7.11, Aflibercept nAMD PSD, May 2024 PBAC Meeting).
- 2.5 The current submission for the PFS provided the full Clinical Study Report (CSR) for the 96-week data set of the PULSAR trial that was considered in May 2024, whereas the last submission provided some draft exposure data for patients treated up to 96 weeks only. The only other changes to the current submission involved updating the cost of the MBS item for intravitreal (IVT) injection and updating the proposed effective price for the aflibercept 8 mg PFS.
- 2.6 The current submission proposed a change to the equi-effective doses recommended by the PBAC for the aflibercept 8 mg vial in May 2024, stating that the sponsor has submitted an application to the TGA for the extended dosing interval based on 96-week treatment data from the PULSAR trial. The submission requested a change to the equi-effective doses previously recommended by the PBAC, assuming that the TGA will allow an extension to the maximum dosing interval out to 20 weeks and that

this would affect the PBAC’s decision. The Pre-Subcommittee Response proposed that any change to the equi-effective doses for the PFS should also be applicable to aflibercept 8 mg vial.

2.7 Information previously reviewed by the PBAC is presented in abbreviated form shaded light blue.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Aflibercept					
Aflibercept solution for intravitreal injection ^a 8 mg pre-filled syringe: 11.43mg/ 0.1mL, 0.1mL syringe	\$934.08 published price \$ [redacted] effective price	1	1	2 (initial) 2 (continuing)	Eylea

^a Each PFS delivers a single dose of 70 µL solution for intravitreal injection containing 8 mg aflibercept.

Initial treatment

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"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
Indication: Subfoveal choroidal neovascularisation (CNV)
Treatment Phase: initial treatment
Clinical criteria:
The condition must be due to age-related macular degeneration
AND
Clinical criteria:
The condition must be diagnosed by optical coherence tomography; or The condition must be diagnosed by fluorescein angiography
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
Treatment criteria:
Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
Administrative Advice:
Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: (1) Details (date, unique identifying number/code or provider number) of the optical coherence tomography or fluorescein angiogram report. If the application is submitted through HPOS form upload or mail, it must include: (a) A completed authority prescription form; and (b) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). All reports must be documented in the patient's medical records.

Continuing treatment

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"/>

Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: Subfoveal choroidal neovascularisation (CNV)
Treatment Phase: Continuing treatment
Clinical criteria:
The condition must be due to age-related macular degeneration
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye
Treatment criteria:
Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist

- 3.1 The submission proposed restrictions for initial and continuing treatment that align with the restrictions for the 8 mg vial. The submission requested an effective AEMP of \$[REDACTED] per 8 mg PFS. The effective AEMP of aflibercept 8 mg vial is \$[REDACTED].

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

4 Population and disease

- 4.1 Age-related macular degeneration (AMD) affects older adults and results in loss of vision because of damage to the macula (the centre of the retina). Neovascular age-related macular degeneration (nAMD), also called wet age-related macular degeneration, is caused by choroidal neovascularisation (CNV). It represents 10-15% of AMD cases.
- 4.2 The submission proposed listing aflibercept 8 mg PFS in the same clinical place in therapy as aflibercept 2 mg, ranibizumab and faricimab for nAMD.
- 4.3 Aflibercept binds to vascular endothelial growth factor 1 and 2 (VEGF-1 and -2) and inhibits the neovascular changes involved in nAMD. Aflibercept in the 2 mg form is PBS listed for patients with nAMD, branch retinal vein occlusion with macular oedema, and DMO.
- 4.4 The proposed recommended dose for aflibercept in the 8 mg PFS form is IVT injection monthly for the first 3 consecutive months (as loading doses). Thereafter, the treatment interval may be extended based on physician's assessment, with the proposed maximum treatment interval being 16 weeks. This is the treatment practice known as 'treat-and-extend' (T&E) whereby the dosing interval for anti-VEGF therapies is increased after the initial stabilisation period; T&E is applied to all IVT anti-VEGF therapies and is commonly employed in Australian clinical practice. Following initial loading doses, the treatment interval is extended by increasing injection intervals in 2- or 4-weekly increments while maintaining stable visual and/or anatomic outcomes.

4.5 There are limited data suggesting that a PFS for IVT injections may be associated with fewer episodes of endophthalmitis than a vial, but most of the data concerns ranibizumab PFS, and there appears to have been a trend to fewer cases of endophthalmitis arising from IVT injections, which complicates assessment of results with recently introduced agents.

4.6 There are limited data suggesting that use of aflibercept PFS may be associated with a higher incidence of acute increases in intra-ocular pressure following IVT injections.

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

5 Comparator

5.1 The submission nominated aflibercept 2 mg as the main comparator. Aflibercept 2 mg was accepted by the PBAC as the appropriate comparator at the May 2024 PBAC meeting, with the PBAC noting that other relevant therapies were faricimab and ranibizumab (Paragraph 7.4, Aflibercept nAMD PSD, May 2024 PBAC Meeting).

5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.3 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: aflibercept 2 mg, faricimab and ranibizumab. Some of these alternative therapies may be less costly than aflibercept 8 mg PFS. The ESC noted that the aflibercept 8 mg vial is also an alternative therapy.

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 The submission was based on the same ongoing randomised head-to-head non-inferiority trial (PULSAR) that was considered by the PBAC in May 2024 in the submission for aflibercept 8 mg vial. The study compared IVT injections of aflibercept

8 mg every 12 weeks (8q12) or every 16 weeks (8q16) with aflibercept 2 mg every 8 weeks (2q8), each after 3 initial monthly injections. In the May 2024 submission, data were available for 60 weeks of treatment; in the current submission data for 96 weeks were provided. The submission claimed that the data also support the extension of the dosing interval to 20 weeks, but as noted above a decision on an extension to the dosing interval has not yet been made by the TGA (see also paragraph 6.17)

6.4 The CANDELA trial was also included in the current submission, as for the May 2024 submission; as noted previously it had a shorter follow-up period than PULSAR, a small sample size, the dosing schedule of aflibercept 2 mg was not aligned with the TGA approved PI and the primary outcomes were safety and pharmacodynamic efficacy. It was not used to support the clinical claim.

6.5 The submission did not provide any clinical evidence related to use of the aflibercept 8 mg in the PFS form.

6.6 Details of the trial presented in the submission is provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PULSAR	Clinical study report: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration.	Report date: 11 Jan 2023
	Clinical study protocol: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration. Version 4.0	Protocol date: 13 September 2022
	Statistical analysis plan: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration. Version 3.0	Report date: 22 August 2022
	Korobelnik JF, Schmidt-Ott UM, Schulze A, Zhang X, Leal S. Tolerability and safety of intravitreal aflibercept 8 mg in the Phase 3 PULSAR trial of patients with neovascular age-related macular degeneration	Investigative Ophthalmology and Visual Science. 2023;64(8):278.
	Lanzetta P, Leal S, Machewitz T, Zhang X. Baseline disease characteristics in patients maintaining q12 and q16 dosing with aflibercept 8 mg versus patients with shortened treatment intervals: A Phase 3 PULSAR post-hoc analysis	Investigative Ophthalmology and Visual Science. 2023;64(8):2239.
	Sivaprasad S, Leal S, Machewitz T, Zhang X. Subgroup analyses from the Phase 3 PULSAR trial of aflibercept 8 mg in patients with treatment-naïve neovascular age-related macular degeneration	Investigative Ophthalmology and Visual Science. 2023;64(8):2238.
	Spitzer MS. Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 48-week results from the Phase 3 PULSAR trial	Investigative Ophthalmology and Visual Science. 2023;64(8):461.
	Wong TY, Heier JS, Zhang X, Schulze A, Machewitz T, Leal S. Intravitreal aflibercept 8 mg in patients with polypoidal choroidal vasculopathy (PCV): A Phase 3 PULSAR trial subgroup analysis	Investigative Ophthalmology and Visual Science. 2023;64(8):2240.

Source: Table 2.3, pp22-24 of the submission.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

6.7 The key features of the direct randomised trial PULSAR are summarised in Table 3. The only difference compared to the submission for the aflibercept 8 mg vial was the provision of the CSR for 96 weeks although some of the 96-week data were reviewed in May 2024.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
PULSAR ^a	1,011	R, DB, MC, Non-inferiority trial Ongoing	Low	Sub-foveal CNV secondary to AMD	Primary: Change in BCVA Key secondary: patients with no IRF and no SRF. NEI-VFQ-25

Source: Table 2.4, pp26-27 of the submission.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: BCVA= best corrected visual acuity, CNV = choroidal neovascularisation, DB = double blind, IRF = intraretinal fluid, MC = multi-centre, AMD= age-related macular degeneration, NEI-VFQ-25= National Eye Institute Visual Function Questionnaire 25, OL = open label, R = randomised, SRF= subretinal fluid.

^a PULSAR is an ongoing trial, with an expected treatment period of approximately 96 weeks in the masked period with an additional 48 weeks in the open label and optional treatment period (final study visit expected at Week 156). The primary analysis was based on data up to Week 48; with the submission presenting outcome data up to Week 96.

6.8 The trial intervention was the 8 mg vial form of aflibercept, not the pre-filled syringe.

6.9 Disposition of patients in the trial, separating the period up to 60 weeks from 60 to 96 weeks, is shown in Table 4. Some patients not completing study treatment at 60 weeks remained in the trial at 60 weeks (60-week CSR, p76) but may have withdrawn before 96 weeks, and, presumably, some patients not completing 96 weeks treatment did not withdraw from the study, and this may account for apparent discrepancies in the numbers of withdrawals.

6.10 There were more withdrawals attributed to death between 60 and 96 weeks than up to 60 weeks. Accounting for the shorter duration, it appears that deaths may have increased in the second period.

Table 4: Disposition of patients at 60 and 96 weeks in the PULSAR trial

	Aflibercept 2 mg		Aflibercept 8 mg			
	2q8 (N = 336)		8q12 (N = 335)		8q16 (N = 338)	
	60 weeks	96 weeks	60 weeks	96 weeks	60 weeks	96 weeks
Completed study treatment	305	287	311	289	309	294
Withdrawals	0-60 weeks	60-96 weeks	0-60 weeks	60-96 weeks	0-60 weeks	60-96 weeks
n (%)	30 (8.9%)	20 (5.9%)	22 (6.5%)	26 (7.7%)	28 (8.3%)	16 (4.7%)
Adverse event, n (%)	5 (1.5%)	2 (0.6%)	4 (1.2%)	2 (0.6%)	5 (1.5%)	2 (0.6%)
Patient decision, n (%)	8 (2.4%)	7 (2.1%)	7 (2.1%)	14 (4.2%)	15 (4.4%)	5 (1.5%)
Death, n (%)	5 (1.5%)	6 (1.8%)	3 (0.9%)	4 (1.2%)	2 (0.6%)	5 (1.5%)
Annualised rate of death	4.3	8.7	4.3	5.8	2.9	7.2
Lack of efficacy, n (%)	2 (0.6%)	0	0	1 (0.3%)	0	0
Other, ¹ n (%)	10 (3.0%)	5 (1.8%)	8 (2.4%)	5 (1.5%)	6 (1.8%)	4 (1.2%)

Source: 60-week CSR, Figure 8-1, p77; 96-week CSR, Figure 8-1, p60.

¹ Includes physician decision, protocol deviations, lost to follow-up, Covid-19 related, and no reason given.

2q8 = 2 mg aflibercept 8-weekly; 8q12 = 8 mg aflibercept 12-weekly; 8q16 = 8 mg aflibercept 16-weekly; NA = not applicable.

- 6.11 Updated data for the extent of exposure is shown in Table 5. Week 48 and 60 data as previously reviewed by the PBAC for the aflibercept 8 mg vial, were summarised in Table 2.13 of the submission. It should be noted that although treatment durations beyond 96 weeks were recorded, injections given after week 96 were not counted.
- 6.12 If only the patients who completed 96 weeks of treatment are considered, the mean number of active injections was 12.8, 9.7 and 8.2 in the 2q8, 8q12 and 8q16 groups respectively (96-week CSR, p96).
- 6.13 All groups started treatment with three injections at monthly intervals, given at baseline and weeks 4 and 8, and the last injection counted in Table 5 was given at week 92 (96-week CSR, Table 7-3, pp29-30). The expected numbers of injections received up to week 96 were, therefore, 13 in the 2q8 group, 10 in the 8q12 group and 8 in the 8q16 group.

Table 5: Extent of exposure through Week 96 in the PULSAR trial

	Aflibercept 2 mg	Aflibercept 8 mg	
	2q8 (N = 336)	8q12 (N = 335)	8q16 (N = 338)
Number of active injections			
Mean (SD)	11.9 (2.4)	9.2 (1.9)	7.8 (2.1)
Median (range)	13.0 (1-14)	9.0 (1-13)	9.0 (0-13)
Number of sham injections			
Mean (SD)	8.5 (2.6)	11.6 (3.2)	12.9 (4.0)
Median (range)	10.0 (0-10)	13.0 (0-14)	15.0 (0-16)
Duration of treatment, weeks			
Mean (SD)	88.9 (19.9)	90.1 (18.4)	89.2 (20.3)
Median (range)	96.0 (4-102)	96.0 (4-102)	96.0 (0-106)

Source: 96-week CSR, Table 10-1, p97 and Table 2.13 p52 of the submission.

Abbreviations: 2q8 = aflibercept 2 mg every 8 weeks; 8q12 = 8 mg of aflibercept every 12 weeks; 8q16 = 8 mg of aflibercept every 16 weeks; NA = not applicable; SD = standard deviation.

6.14 Changes in administration frequency were allowed in patients randomised to 8q12 or 8q16 if pre-defined dose regimen modification (DRM) criteria were met.

6.15 The DRM criteria were:

- for shortening of the dosage interval, greater than five letter loss in best corrected visual acuity from week 12, and a greater than 25 µm increase in central retinal thickness from week 12 or new foveal haemorrhage or new foveal neovascularisation;
- for lengthening of the dosage interval, less than five letter loss in best corrected visual acuity from week 12 and no fluid at the central subfield on OCT and no new onset foveal haemorrhage/foveal neovascularisation.

6.16 It is noted that these were efficacy criteria, not tolerability criteria – i.e., dose intervals could not be shortened for adverse events.

6.17 From Week 16 to Week 52, treatment intervals could only be shortened, in four weeks decrements to a minimum of 8 weeks. From Week 52, dosing intervals could be shortened or lengthened by four weeks, with the change coming into effect at or after the Week 60 visit.

6.18 Changes in administration frequency among patients completing 96 weeks treatment are shown in Table 6. The 96-week data provide limited information about treatment at 20-week intervals. Of patients randomised to 8 mg doses, 277 (47.5%) had the treatment interval lengthened to 20 weeks. Because lengthening of the treatment interval could be decided on no earlier than the week 52 visit, the maximum number of injections received up to the week 96 data cut-off at intervals of 20 weeks or longer was two, since patients in the aflibercept 8q16 group who met the DRM criteria for treatment interval lengthening to 20 weeks at 52 weeks would have had injections at 72 and 92 weeks. Patients whose interval was lengthened to 20 weeks at the week 56 visit but before week 76 would have received only one injection before the week 96 cut-off. Patients who met the criteria for lengthening to 20 weeks after 76 weeks could not receive an injection at the longer interval before the data cut-off. The numbers

whose dose interval was lengthened to 20 weeks after 56 and 76 weeks were not provided, but there were 48 (17.3%) who only met the criteria at the last visit.

Table 6: Changes in administration frequency of aflibercept 8 mg in patients completing 96 weeks in the PULSAR trial

	Aflibercept 8 mg	
	8q12 (N = 291)	8q16 (N = 292)
Treatment interval was shortened at any time, n (%)	77 (26.5%)	90 (30.8%)
Treatment interval was lengthened at any time, n (%)	214 (73.5%)	187 (64.0%)
Treatment interval was lengthened to 20 weeks, n (%)	119 (40.9%)	158 (54.1%)
Treatment interval was lengthened to 20 weeks then shortened, n (%)	1 (0.3%)	3 (1.0%)
Treatment interval was lengthened to 20 weeks and maintained at 20 weeks, n (%)	17 (5.8%)	46 (15.8%)
Treatment interval was lengthened to 20 weeks and lengthened again to 24 weeks, n (%)	72 (24.7%)	90 (30.8%)
Treatment interval was lengthened to 20 weeks at last visit, n (%)	29 (10.0%)	19 (6.5%)

Source: 96-week CSR, Table 10-2, pp99-100. 8q12 = aflibercept 8mg 12-weekly; 8q16 = 8 mg aflibercept 16-weekly.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Comparative effectiveness

6.19 The results from PULSAR for the primary outcome, change from baseline in best corrected visual acuity (BCVA) at week 48 and the secondary outcome, change from baseline in BCVA at week 60 are summarised in Table 7 and Figure 1. In all instances of comparison (at week 48, 60 and 96, between 2q8 versus 8q12 and 8q16), the 95% CI included 0, indicating treatment differences were not statistically significant. The p-values were statistically significant and the lower 95% confidence limits of the treatment differences were within the non-inferiority limit of 4 letters, thereby meeting the pre-specified non-inferiority margin.

Table 7: Results of BCVA in the PULSAR trial (FAS; MMRM)

	Aflibercept 8 mg		Aflibercept 2 mg	Estimate for contrast (95% CI) ^a	
	8q12 (N=335)	8q16 (N=338)	2q8 (N=336)	Non-inferiority p-values ^b	
				8q12 vs 2q8	8q16 vs 2q8
Mean baseline BCVA (ETDRS letter score)	59.9	60.0	58.9		
Week 48					
Patients with data (%)	299 (89.3%)	289 (85.5%)	285 (84.8%)	-0.97 (-2.87, 0.92) 0.0009	-1.14 (-2.97, 0.69) 0.0011
Mean change from baseline in BCVA (SD)	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)		
LS mean change from baseline in BCVA (SE)	6.06 (0.77)	5.89 (0.72)	7.03 (0.74)		
Week 60					
Patients with data (%)	283 (84.5%)	282 (83.4%)	268 (79.7%)	-0.86 (-2.57, 0.84) 0.0002	-0.92 (-2.51, 0.66) <0.0001
Mean change from baseline in BCVA (SD)	6.6 (13.6)	6.6 (11.7)	7.8 (12.6)		
LS mean change from baseline in BCVA (SE)	6.37 (0.74)	6.31 (0.66)	7.23 (0.68)		
Week 96					
Patients with data (%)	256 (76.4%)	264 (78.1%)	243 (72.3%)	-1.01 (-2.82, 0.80) 0.0006	-1.08 (-2.87, 0.71) 0.0007
Mean change from baseline in BCVA (SD)	5.9 (14.2)	5.6 (13.7)	7.4 (13.8)		
LS mean change from baseline in BCVA (SE)	5.59 (0.77)	5.52 (0.75)	6.60 (0.73)		

Source: Table 2.17, p63 and Table 2.18, p65-67 of the submission.

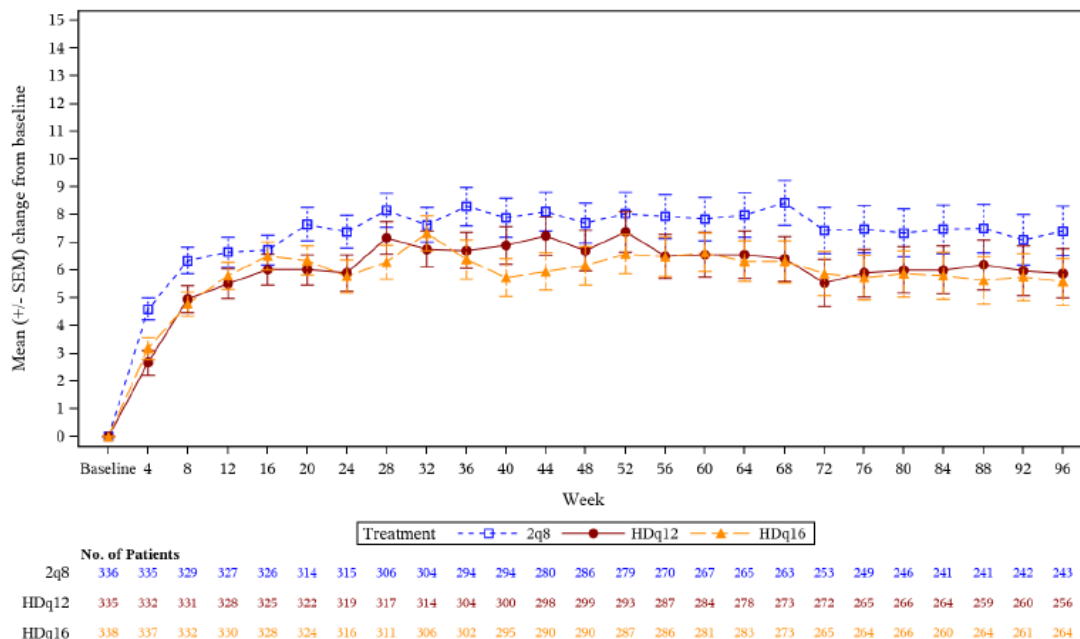
Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: 2q8= aflibercept 2 mg administered every 8 weeks, 8q12 = aflibercept 8 mg administered every 12 weeks, 8q16 = aflibercept 8 mg administered every 16 weeks; BCVA. = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study, BCVA = best corrected visual acuity, CI = confidence interval, FAS= full analysis set, LS = least squares, MMRM = mixed model for repeated measurements, N = total number of participants in treatment arm, SD = standard deviation, SE = standard error.

^a Estimate for contrast was based on the MMRM model with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs rest of world]; baseline BCVA [< 60 vs ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit, computed for the differences of aflibercept 8q12 minus 2q8 and 8q16 minus 2q8, respectively with 2-sided 95% CIs

^b p-value for the 1-sided non-inferiority test at a margin of 4 letters

Figure 1: Mean change from baseline in BCVA score through week 96, OC prior to ICE (FAS)



Source: Figure 2-8, p66 of the submission.

Abbreviations: OC = observed cases, BCVA = best corrected visual acuity, FAS = full analysis set, ICE = intercurrent event

- 6.20 Results of the secondary outcome, mean National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) are presented in Table 8. As noted previously, an improvement in quality of life as measured by the mean change from baseline in the NEI-VFQ-25 score from baseline was comparable across treatment arms.
- 6.21 Although reduced burden on patients having less frequent injections was part of the rationale for high-dose aflibercept (60-week CSR, p10), it is not surprising that no effect on measured quality-of-life was seen in the PULSAR trial. None of the 12 subscales of the NEI-VFQ-25 refer to treatment administration, and the total number of injections (active + sham) was the same in all groups. Because injections were given by unblinded staff there may have been differences between them perceptible to patients, but no data are provided on this point.

Table 8: Change from baseline in NEI-VFQ-25 total score in the PULSAR trial (FAS; MMRM)

	Aflibercept 8 mg		Aflibercept 2 mg	Estimate for contrast (95% CI) ^a Nominal p-value for superiority test	
	8q12 (N=335)	8q16 (N=338)	2q8 (N=336)	8q12 vs 2q8	8q16 vs 2q8
Mean NEI-VFQ-25 score at baseline	76.4	77.7	77.8		
Week 48					
Patients with data (%)	285 (85.1%)	266 (78.7%)	266 (79.2%)	-0.72 (-2.35, 0.90) 0.3817	-0.87 (-2.55, 0.80) 0.3070
Mean change from baseline (SD)	4.1 (10.4)	3.4 (10.8)	4.6 (11.0)		
LS mean change from baseline (SE)	3.50 (0.70)	3.35 (0.72)	4.22 (0.70)		
Week 60 (OC)					
Patients with data (%)	268 (80.0%)	257 (76.0%)	254 (75.6%)	NR	NR
Mean change from baseline (SD)	3.65 (12.08)	3.84 (11.89)	5.10 (11.38)		
LS mean change from baseline (SE)	NR	NR	NR		
Week 96 (OC prior to ICE)					
Patients with data (%)	245	247	229	NR	NR
Mean change from baseline (SD)	2.72 (12.65)	2.64 (12.39)	4.16 (11.93)		
LS mean change from baseline (SE)	NR	NR	NR		

Source: Table 2.25, p75 of the submission.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: 2q8 = aflibercept 2 mg administered every 8 weeks, BCVA = best corrected visual acuity, CI = confidence interval, FAS = full analysis set, 8q12 = aflibercept 8 mg administered every 12 weeks, 8q16 = aflibercept 8 mg administered every 16 weeks, LS = least squares, MMRM = mixed model for repeated measurements, N = total number of participants in treatment arm, NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire 25, NR = not reported, OC = observed cases, SD = standard deviation, SE = standard error, ICE = intercurrent event.

^a Estimate for contrast was based on the MMRM model with baseline NEI-VFQ-25 total score as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs rest of world]; baseline BCVA [< 60 vs ≥ 60]) as fixed factors, and terms for the interaction between baseline NEI-VFQ-25 total score and visit and the interaction between treatment and visit, computed for the differences of aflibercept 8q12 minus 2q8 and 8q16 minus 2q8, respectively with 2-sided 95% CIs

Comparative harms

- 6.22 The submission did not present any safety data from the use of the PFS product.
- 6.23 The submission did not present the 96-week safety data for the PULSAR trial; Table 9 presents the results extracted from the 96-week CSR for the outcomes that were presented in the previous submission.
- 6.24 There were discrepancies in the data for adjudicated Anti-Platelet Trialists Collaboration (APTCL) events in the 96-week CSR; Table 10-3 and Table 10-16 give different numbers of events, although the corresponding tables in the 60-week CSR (Tables 10-3 and 10-17) give identical numbers.
- 6.25 The number of adverse events related to IVT injection procedures was similar in all groups. However, the CSR did not present results separately for active and sham injections, which may favour trial arms with fewer active injections. Sham and active injections were given by unblinded staff, and sham injections were mock injections,

using a syringe with no needle, so blinding of patients may not have been complete and not all adverse events were equally likely with active and sham injections.

- 6.26 Adverse events reported for the 96-week data set but not for the 60-week data set are shown in Table 10. Because a study treatment was given at week 60, and treatment emergent adverse events included events up to 30 days after the last treatment, it is not clear what time periods are covered by the two data sets. However, an exploratory calculation (done during the evaluation) of an annualised rate for some adverse events is given based on the assumption of 60 weeks and 96 weeks exposure and is shown in Table 10.
- 6.27 The rate of adverse events associated with IVT injections and the rate of adverse events leading to discontinuation appear to have been lower in the period 60-96 weeks than in the period up to 60 weeks.
- 6.28 There appears to have been an increased rate of adverse events leading to death, and of adjudicated cardiovascular death, in the period 60-96 weeks compared to the period up to 60 weeks. A similar difference was noted for withdrawals due to death (see paragraph 6.8). The ESC considered that the sponsor should address this in their pre-PBAC response.
- 6.29 Data for all adjudicated APTC events are difficult to interpret because of the discrepancy in data between Tables 10-3 and 10-16 in the 96-week CSR, but if the Table 10-16 data are correct there appears to have been an increase, and if the Table 10-3 data are correct there was a dramatic increase, in weeks 60-96.
- 6.30 All of the differences between 0 to 60 weeks and 60 to 96 weeks were seen in all treatment groups.

Table 9: Summary of adverse events in the PULSAR trial

	96 weeks			60 weeks		
	Aflibercept 8 mg		Aflibercept 2 mg	Aflibercept 8 mg		Aflibercept 2 mg
	8q12 (N=335) n (%)	8q16 (N=338) n (%)	2q8 (N=336) n (%)	8q12 (N=335) n (%)	8q16 (N=338) n (%)	2q8 (N=336) n (%)

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Any AE	294 (87.8%)	306 (90.5%)	302 (89.9%)	258 (77.0%)	278 (82.2%)	263 (78.3%)
Any study drug-related TEAE	23 (6.9%)	22 (6.5%)	24 (7.1%)	20 (6.0%)	15 (4.4%)	18 (5.4%)
Any study drug-related ocular TEAE	21 (6.3%)	19 (5.6%)	17 (5.1%)	18 (5.4%)	13 (3.8%)	13 (3.9%)
Any TEAE related to intravitreal injection procedure	44 (13.1%)	46 (13.6%)	51 (15.2%)	38 (11.3%)	40 (11.8%)	45 (13.4%)
Any TEAE leading to discontinuation	6 (1.8%)	6 (1.8%)	9 (2.7%)	5 (1.5%)	6 (1.8%)	8 (2.4%)
Any ocular TEAE leading to discontinuation	4 (1.2%)	4 (1.2%)	4 (1.2%)	4 (1.2%)	4 (1.2%)	2 (0.6%)
Any SAE	91 (27.2%)	78 (23.1%)	76 (22.6%)	52 (15.5%)	50 (14.8%)	61 (18.2%)
Any ocular serious TEAE	11 (3.3%)	12 (3.6%)	6 (1.8%)	8 (2.4%)	8 (2.4%)	6 (1.8%)
Any serious TEAE in the study eye	10 (3.0%)	10 (3.0%)	4 (1.2%)	7 (2.1%)	7 (2.1%)	4 (1.2%)
Any TEAE	292 (87.2%)	303 (89.6%)	300 (89.3%)			
Any serious TEAE related to intravitreal injection procedure	3 (0.9%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)
Any AE with outcome death	10 (3.0%)	7 (2.1%)	12 (3.6%)	3 (0.9%)	2 (0.6%)	5 (1.5%)
Any TEAE of intraocular inflammation in study eye	7 (2.1%)	6 (1.8%)	3 (0.9%)	4 (1.2%)	1 (0.3%)	4 (1.2%)
Any treatment-emergent APTC by Table 10-3	24 (7.2%)	15 (4.4%)	18 (5.4%)	1 (0.3%)	2 (0.6%)	8 (2.4%)
Any treatment-emergent APTC by Table 10-17/16	5 (1.5%)	7 (2.1%)	11 (3.3%)	1 (0.3%)	2 (0.6%)	8 (2.4%)
Cardiovascular death	3 (0.9%)	2 (0.6%)	5 (1.5%)	0	1 (0.3%)	2 (0.6%)
Non-fatal myocardial infarction	1 (0.3%)	4 (1.2%)	4 (1.2%)	0	1 (0.3%)	4 (1.2%)
Non-fatal stroke	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	2 (0.6%)
Any TEAE of hypertension	27 (8.1%)	28 (8.3%)	27 (8.0%)	19 (5.7%)	18 (5.3%)	12 (3.6%)

Source: 96-week CSR, Table 10-3, p102-104; Table 10-17, p132; 60 weeks CSR, Table 10-3, pp158-159; Table 10-16, p183.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: 2q8 = aflibercept 2 mg administered every 8 weeks, 8q12 = aflibercept 8 mg administered every 12 weeks, 8q16 = aflibercept 8 mg administered every 16 weeks, AE = adverse event, APTC = Anti-Platelet Trialists Collaboration; CI = confidence interval, IVT = intravitreal, n = number of participants with event, N = total number of participants in treatment arm, OR = odds ratio, RD = risk difference, SAE = serious adverse event, SAF = safety analysis set, TEAE = treatment-emergent adverse events.

TEAEs are defined as AEs that started in the time from first injection to the last injection (active or sham) in the study plus 30 days. Post-treatment AEs are defined as AEs that started more than 30 days after the last injection (active or sham) in the study.

Table 10: Selected additional adverse events reported in the 96-week CSR compared to the 60-week CSR for the PULSAR trial

	Aflibercept 8 mg				Aflibercept 2 mg	
	8q12 (N = 335)		8q16 (N = 338)		2q8 (N = 336)	
	60 weeks	60-96 weeks	60 weeks	60-96 weeks	60 weeks	60-96 weeks
Any TEAE related to intravitreal injection procedure, n (rate per year)	38 (33.1)	6 (8.6)	40 (34.8)	6 (8.64)	45 (39.2)	6 (8.6)
Any TEAE leading to discontinuation, n (rate per year)	5 (4.4)	1 (1.4)	6 (5.2)	0	8 (7.0)	1 (1.4)
Any serious TEAE in the study eye, n (rate per year)	7 (6.1)	3 (4.3)	7 (6.1)	3 (4.3)	4 (3.5)	0
Any AE with outcome death, n (rate per year)	3 (2.6)	7 (10.1)	2 (1.7)	5 (7.2)	5 (4.4)	7 (10.1)
Any treatment emergent adjudicated APTC by Tables 10-16/17, n (rate per year)	1 (0.9)	4 (5.8)	2 (1.7)	5 (7.2)	8 (7.0)	3 (4.3)
Any treatment emergent adjudicated APTC by Table 10-3, n (rate per year)	1 (0.9)	23 (33.1)	2 (1.7)	13 (18.7)	8 (7.0)	10 (14.4)
Adjudicated cardiovascular death, n (rate per year)	0	3 (4.3)	1 (0.9)	1 (1.4)	2 (1.7)	3 (4.3)
Any TEAE of hypertension, n (rate per year)	19 (16.5)	8 (11.5)	18 (15.7)	10 (14.4)	12 (10.4)	15 (21.6)

Source: Data from Table 9 and calculated from data in the CSR during the evaluation.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: 2q8 = 2 mg aflibercept 8-weekly; 8q12 = 8 mg aflibercept 12-weekly; 8q16 = 8 mg aflibercept 16-weekly; AE = adverse event; TEAE = treatment emergent adverse event; APTC = Anti-Platelet Trialists Collaboration.

6.31 The submission provided data in support of the claim that use of a PFS is associated with lower rates of endophthalmitis. Taken as a whole, the data are consistent with an association of lower rates of endophthalmitis with use of PFS, but causation has not been established. Some data suggest that endophthalmitis may be less frequent with ranibizumab PFS than with aflibercept PFS.

6.32 There may be an increased risk of acute rises in intra-ocular pressure with use aflibercept PFS. This risk was not discussed in the submission.

Benefits/harms

6.33 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.34 The submission described aflibercept 8 mg PFS as non-inferior in effectiveness compared to aflibercept 2 mg. This claim has previously been accepted by the PBAC.

6.35 The submission described aflibercept 8 mg PFS as non-inferior in terms of safety compared to aflibercept 2 mg, with a reduced injection burden. The claim of non-

inferior safety has been previously accepted by the PBAC, but as noted above, there are no clinical data that use the PFS product.

- 6.36 There were no data in the submission from which comparative effectiveness and safety of the 8 mg vial preparation versus the PFS could be assessed. As the PFS has been approved by the TGA, effectiveness and safety would be expected to be the same. The injection burden would be the same for these two presentations.
- 6.37 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.38 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.39 The submission presented a CMA, comparing aflibercept 8 mg PFS to aflibercept 2 mg, as presented in the submission for the 8 mg vial. The key assumptions and components of the CMA are presented in Table 11 and were unchanged from the initial CMA proposed in May 2024 other than updating the MBS scheduled fee for the IVT injection.

Table 11: Key assumptions and components of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2 of the submission, aflibercept 8 mg PFS is non-inferior in effectiveness to aflibercept 2 mg
Therapeutic claim: safety	Based on evidence presented in Section 2 of the submission, aflibercept 8 mg PFS is non-inferior in safety to aflibercept 2 mg
Evidence base	Direct randomised trial ¹ PULSAR
Equi-effective doses	Year 1: 6.17 doses of aflibercept 8 mg PFS annually to 7.89 doses of aflibercept 2 mg annually Year 2: 3.94 doses of aflibercept 8 mg PFS annually to 6.12 doses of aflibercept 2 mg annually.
Direct medicine costs	Calculated from equi-effective doses accounting for drug (effective AEMP) and administration costs (MBS fees)
Other costs or cost offsets	Administration costs: MBS item 42738 – Fee = \$342.65

Source: Table 3.2, p111 of the submission. Abbreviations: PFS = pre-filled syringe; AEMP, approved ex-manufacturer price; MBS, Medicare Benefits Schedule

- 6.40 In this submission, the equi-effective doses were estimated as the same as those originally proposed in May 2024:
- Year 1: 6.17 dose of aflibercept 8 mg PFS to 7.89 doses of aflibercept 2 mg
 - Year 2: 3.94 doses of aflibercept 8 mg PFS to 6.12 doses of aflibercept 2 mg.
- 6.41 This dose equivalence was the same as that originally proposed in the May 2024 submission. The equi-effective doses were not as recommended by the PBAC in May 2024, which were, over 2 years 11.50 doses of aflibercept 8 mg/faricimab and 14.00 doses of aflibercept 2 mg/ranibizumab, as follows:
- Year 1: 7.20 injections of aflibercept 8 mg/faricimab to 7.69 injections of aflibercept 2 mg/ranibizumab

- Year 2: 4.30 injections of aflibercept 8 mg/faricimab to 6.31 injections of aflibercept 2 mg/ranibizumab.

6.42 This submission did not provide any data that could be used to change these estimates, although the submission stated that there would be a TGA application for the extension of the duration of the dosing interval for aflibercept 8 mg to 20 weeks. At the time of the evaluation, this application had not been evaluated. The ESC noted the change to the PI to allow extension to 20 weeks is not expected until [REDACTED].

6.43 The updated CMA presented in the current submission is shown in Table 12.

Table 12: Results of cost-minimisation approach - November 2024 submission

Row	Parameter	Aflibercept 8 mg PFS	Aflibercept 2 mg	Reference /Calculation
A	Drug costs per administration (AEMP)	\$ [REDACTED]	\$ [REDACTED]	Aflibercept 2 mg: known to sponsor Aflibercept 8 mg: Calculated ((F – E) / B)
B	Administration frequency - two-year analysis period	10.10	14.01	Aflibercept 2 mg: DUSC analysis (Primary analysis, Table 3-6. Aflibercept 8 mg: PULSAR RCT
C	Total drug costs (AEMP)	\$ [REDACTED]	\$ [REDACTED]	A x B
D	Administration (unit cost)	\$342.65		MBS item: 42738
E	Total administration costs	\$3,462.28	\$4,800.53	D x B
F	Total drug and administration costs	\$ [REDACTED]	\$ [REDACTED]	C + E

Source: Table 3.7, p119 of the submission.

Abbreviations: PFS = pre-filled syringe; AEMP, approved ex-manufacturer price; DUSC, Drug Utilisation Sub Committee; MBS, Medicare Benefits Schedule; RCT, randomised controlled trial

6.44 No evidence was provided that 8 mg aflibercept PFS provides a significant improvement in efficacy and/or reduction in safety over aflibercept 2 mg or aflibercept 8 mg vial, faricimab or ranibizumab.

Drug cost/patient /year

6.45 The updated estimate of the drug cost per patient per year is shown in Table 13.

Table 13: Drug cost per patient for proposed and comparator drugs

	Aflibercept 8 mg trial dose and duration	Aflibercept 8 mg CMA	Aflibercept 8 mg financial estimates	Aflibercept 2 mg trial dose and duration	Aflibercept 2 mg CMA	Aflibercept 2 mg financial estimates
Mean dose/scripts	4.99 doses ^a	5.195 doses ^b	5.195 doses ^b	6.98 doses ^c	7.01 doses ^d	7.01 doses ^d
DPMQ per script		\$ [REDACTED]			\$ [REDACTED]	
Cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: updated from Table 10, PSD May 2024 PBAC Meeting.

Note: Shaded information is unchanged from the submission for aflibercept 8 mg vial.

Abbreviations: CMA= cost-minimisation approach, mg = milligrams.

^a Averaged over 2-years treatment (6.17 doses in Year 1 and 3.82 doses in Year 2, including the 24-week treatment interval).

^b Averaged over 2-years treatment, assuming a maximum treatment interval of 16 weeks as proposed in the TGA Delegate's Overview (6.17 doses in Year 1 and 4.22 doses in Year 2).

^c Average of the total number of doses (13.95 doses) estimated per patient at the week 96 data cut, adjusted for treatment duration and apportioned to two years (104 weeks).

^d Averaged over 2-years treatment (7.89 doses in Year 1 and 6.12 doses in Year 2).

Estimated PBS usage & financial implications

- 6.46 This submission was not considered by DUSC.
- 6.47 The submission presented the same market share approach and financial estimates model as that used in the May 2024 submission for the aflibercept 8 mg vial. The only change to the estimates was the use of the updated MBS fee for IVT injections, and a small change to the proposed effective price for aflibercept 8 mg PFS.
- 6.48 The estimates of use did not differentiate between the 8 mg vial and the 8 mg PFS. The submission assumed all patients would receive the PFS.
- 6.49 The updated estimates of financial impact of listing, using the proposed effective price of the aflibercept 8 mg PFS are shown in Table 14.

Table 14: Net financial implications to the PBS/RPBS of the proposed listing of aflibercept 8 mg for nAMD, effective pricing

Year	2025	2026	2027	2028	2029	2030
Total aflibercept 8 mg scripts						
PBS/RPBS total	1	2	3	4	5	5
Total financial impact (less co-pay)						
PBS/RPBS total	6	7	8	9	10	10
Changes in financial impact of other medicines (less co-pay)						
PBS/RPBS total	11	11	11	11	11	11
Net financial impact (less co-pay)						
PBS/RPBS total	12	13	13	13	13	13
Net cost to MBS	11	11	11	11	11	11
Net cost to Government	12	12	12	11	11	11

Source: Tables 4.24, 4-29 p 137, 141 of the submission.

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule.

The redacted values correspond to the following ranges:

1 30,000 to < 40,000

2 50,000 to < 60,000

3 70,000 to < 80,000

4 90,000 to < 100,000

5 100,000 to < 200,000

6 \$20 million to < \$30 million

7 \$40 million to < \$50 million

8 \$60 million to < \$70 million

9 \$80 million to < \$90 million

10 \$100 million to < \$200 million

11 net cost saving

12 \$0 to < \$10 million

13 \$10 million to < \$20 million

- 6.50 The total cost to the PBS/RPBS of listing aflibercept 8 mg PFS was estimated to be \$20 million to < \$30 million in Year 1 and a total of \$400 million to < \$500 million in the first 6 years of listing. After accounting for substitution of aflibercept 2 mg and faricimab, the estimated net cost was \$0 to < \$10 million in Year 1 and \$60 million to < \$70 million in the first 6 years of listing. The ESC noted the financials included a net cost to the Government in the first few years, likely driven by initiating

patients requiring loading doses, and a net save in later years due to the dosing interval extension.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of aflibercept 8 mg pre-filled syringe (PFS) for the treatment of patients with sub-foveal choroidal neovascularisation secondary to age-related macular degeneration. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of aflibercept 8 mg PFS would be acceptable if it were cost-minimised to the lowest cost PBS-listed anti-VEGF treatment for the same indication.
- 7.2 The PBAC noted that the submission did not provide any clinical data that specifically related to the PFS, and that the submission used the same data package (with updated trial data) that had been used when the Committee considered aflibercept 8 mg vial in May 2024.
- 7.3 The PBAC recalled it had previously accepted the claim that aflibercept 8 mg was non-inferior in terms of comparative efficacy and safety versus aflibercept 2 mg.
- 7.4 The PBAC considered that the equi-effective doses for the aflibercept 8 mg vial recommended at the May 2024 PBAC meeting remain appropriate for the 8 mg PFS, noting that over 2 years these are 11.50 doses of aflibercept 8 mg/faricimab and 14.00 doses of aflibercept 2 mg/ranibizumab, as follows:
 - Year 1: 7.20 injections of aflibercept 8 mg/faricimab to 7.69 injections of aflibercept 2 mg/ranibizumab
 - Year 2: 4.30 injections of aflibercept 8 mg/faricimab to 6.31 injections of aflibercept 2 mg/ranibizumab.
- 7.5 The PBAC noted it would be unable to consider amending the equi-effective doses until the change to the Product Information to include a 20-week dosing interval had been approved by the TGA.
- 7.6 The PBAC considered that the listing would be cost-neutral to the PBS/RPBS.
- 7.7 The PBAC considered that a grandfather restriction was appropriate and that it should be in operation for a maximum of 12 months from listing.
- 7.8 The PBAC advised, under Section 101 (4AACD) of the *National Health Act*, that aflibercept 8 mg vial and aflibercept 8 mg pre-filled syringe 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).
- 7.9 The PBAC advised that aflibercept 8 mg PFS is not suitable for prescribing by nurse practitioners.

- 7.10 The PBAC recommended that the Early Supply Rule should not apply.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because aflibercept 8 mg PFS is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over aflibercept 2 mg, 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 2022* for Pricing Pathway A were not met.
- 7.12 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 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
AFLIBERCEPT					
Initial treatment					
aflibercept 8 mg/0.07 mL injection, 0.07 mL syringe	NEW	1	1	2	Eylea
Continuing treatment					
aflibercept 8 mg/0.07 mL injection, 0.07 mL syringe	NEW	1	1	2	Eylea
Restriction Summary edit / Treatment of Concept: edit					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: Authority Required (in writing - legacy) – Postal/HPOS upload or Online PBS Authorities immediate assessment					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.					
Administrative Advice: Where both eyes are affected by the condition, a quantity of 2 units can be requested through the same authority application.					
Administrative Advice: Pharmaceutical benefits that have the form aflibercept 0.07mL injection syringe and pharmaceutical benefits that have the form aflibercept 0.07 mL injection vial are equivalent for the purposes of substitution.					
Indication: Subfoveal choroidal neovascularisation (CNV)					

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	Treatment Phase: Initial treatment
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD)
	AND
	Clinical criteria:
	The condition must be diagnosed by optical coherence tomography; or
	The condition must be diagnosed by fluorescein angiography
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	Prescribing Instructions: Authority approval for initial treatment of each eye must be sought.
	Prescribing Instructions: The first authority application for each eye must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: (1) Details (date, unique identifying number/code or provider number) of the optical coherence tomography or fluorescein angiogram report. If the application is submitted through HPOS form upload or mail, it must include: (a) details of the proposed prescription; and (b) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). All reports must be documented in the patient's medical records.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept:	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]
	Indication: Subfoveal choroidal neovascularisation (CNV)
	Treatment Phase: Continuing treatment
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist

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	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD)
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Restriction Summary edit / Treatment of Concept: edit	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	<input checked="" type="checkbox"/> Authority Required (in writing - legacy) – Postal/HPOS upload or Online PBS Authorities immediate assessment
	Indication: Subfoveal choroidal neovascularisation (CNV)
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this PBS indication for the same eye prior to [PBS listing date],
	AND
	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD),
	AND
	Clinical criteria:
	The condition must be diagnosed by optical coherence tomography; OR
	The condition must be diagnosed by fluorescein angiography,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	Prescribing instruction: The first authority application for each eye must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail and must include: (1) Details (date, unique identifying number/code or provider number) of the optical coherence tomography or fluorescein angiogram report. If the application is submitted through HPOS form upload or mail, it must include: (a) details of the proposed prescription; and (b) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). All reports must be documented in the patient's medical records.

	<p>Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>
	<p>Administrative advice: Patients may qualify for PBS-subsidised treatment under this restriction once only per eye. For continuing PBS-subsidised treatment, a 'Grandfather' patient must qualify under the 'Continuing treatment' criteria.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

- 8.2 Flow-on changes to the Administrative Advice for aflibercept 8 mg vial [14594D, 14626T] will be required to allow for interchangeability with aflibercept 8 mg pre-filled syringe.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.