5.02 AFLIBERCEPT, Solution for intravitreal injection 11.43 mg in 100 microlitres (114.3 mg per mL), Eylea®, Bayer Australia Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required listing for aflibercept 8 mg for the treatment of visual impairment caused by subfoveal choroidal neovascularisation secondary to age-related macular degeneration (nAMD).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus aflibercept 2 mg. The key components of the issues addressed in the submission are summarised in Table 1.

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 subfoveal choroidal neovascularisation secondary to age-related macular degeneration
Intervention	Aflibercept 8.0 mg intravitreal injection
Comparator	Aflibercept 2.0 mg intravitreal injection
Outcomes	Best corrected visual acuity (BCVA), quality of life, safety
Clinical claim	In patients with subfoveal choroidal neovascularisation due to age-related macular degeneration, aflibercept 8 mg is non-inferior in terms of efficacy and safety compared to aflibercept 2 mg

Source: Table 1.2, p28 of the submission.

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

2 Background

Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA)/PBAC parallel process. At the time of the evaluation, no TGA documents were available. The TGA Delegate's Overview was provided prior to consideration by the PBAC. The TGA Delegate was supportive of registering aflibercept 8 mg for the treatment of adults with neovascular (wet) age-related macular degeneration (AMD).

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

3 Requested listing

MEDICINAL PRODUCT Form	DPMQ	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Initial and Continuation					
Aflibercept solution for intravitreal injection 8 mg vial: 11.43mg/ 0.1mL, 0.1mL vial 8 mg pre-filled syringe: 11.43 mg/ 0.1 mL, 0.1 mL syringe	$[redacted] effective price $1,297.17 published price	1	1	2	Eylea

Category/Program	Section 85 – General Schedule
Prescriber type	Medical Practitioners
Indication	Subfoveal choroidal neovascularisation (CNV)
Treatment Phase	**Initial treatment**
Restriction	Authority required – In Writing
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 **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
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.
Treatment Phase	**Continuing treatment**
Restriction	Streamlined
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 **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

Source: Table 1.6, p12, and Table 1.7 and Table 1.8, p13 of the submission.
Abbreviations: DPMQ = dispensed price for maximum quantity, Max = maximum, mL= millilitre, mg= milligram, No. = number, qty = quantity.
Updated during the evaluation (from $[redacted] effective and $1,296.57 published) using the updated scheduled fee for intravitreal injection (MBS item 42738).

3.1 The submission proposed a Special Pricing Arrangement (SPA), with an effective ex-manufacturer price of $ and a published ex-manufacturer price of $1,173.08.

3.2 The submission requested PBS listing for both vial and pre-filled syringe forms of aflibercept 8 mg. However, a TGA application to register the pre-filled syringe presentation had not been submitted prior to lodgement of this submission. Therefore, the syringe presentation was not considered by the PBAC.

3.3 The submission requested grandfathering provisions, estimating that there are < 500 Australian patients from the PULSAR trial, that are likely to be eligible for aflibercept 8 mg under the grandfathering provisions.

3.4 The proposed restrictions are consistent with the current PBS restrictions for aflibercept 2 mg, ranibizumab and faricimab for nAMD but broader than the inclusion criteria in the pivotal trial (PULSAR) that included only treatment-naïve patients.

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

4 Population and disease

4.1 Age-related macular degeneration (AMD) is a medical condition that affects older adults and results in a loss of vision in the centre of the visual field because of damage to the centre of the retina (the macula). Neovascular age-related macular degeneration (nAMD) or wet age-related macular degeneration, which is caused by choroidal neovascularisation (CNV), is a more aggressive form of AMD and represents 10-15% of AMD cases.

4.2 The submission proposed listing aflibercept 8 mg in the same clinical place in therapy as aflibercept 2 mg, ranibizumab and faricimab for nAMD.

4.3 Aflibercept is a recombinant fusion protein that binds to vascular endothelial growth factor (VEGF)- 1 and 2 and to placental growth factor receptors with high affinity, blocking their interaction with endogenous VEGF receptors thereby, inhibiting the angiogenesis, vascular permeability and inflammation involved in nAMD disease progression. 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 form is intravitreal (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 (based on the recommendation in the TGA Delegate's Overview). Treat-and-extend (T&E) is a commonly employed regimen for anti-VEGF therapies in Australian clinical practice, in which, 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 The ESC considered the requirement for loading doses of aflibercept 8 mg in patients already established on other VEGF-I therapies imposes an additional burden on patients and may not always be administered. The ESC considered that this could impact on efficacy.

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. The main arguments provided in support of this nomination were:

- Aflibercept 2 mg is the most frequently prescribed therapy for nAMD based on PBS prescription data, accounting for 69% of prescriptions in 2022/23. It is therefore considered the most likely therapy that would be replaced in clinical practice. Ranibizumab, the next most commonly prescribed first-line therapy, accounted for 26% of prescriptions in 2022/23, and its market share has been declining since 2019. Faricimab (listed on the PBS on the 1 February 2023) accounted for 5% of prescriptions in 2022/23.
- Aflibercept 2 mg is biochemically identical to aflibercept 8 mg (the latter at a higher dose).

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. 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.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinicians stated that in Australia the treat and extend (T&E) paradigm is widely used, that the potential for longer durability with aflibercept 8 mg is clinically relevant for patients in metropolitan and rural/remote settings, and that a lower injection frequency will reduce the burden of access to treatment, including transport, carer and out of pocket costs.

- With respect to switching patients currently on VEGF-I therapy, one clinician suggested that he would switch nearly all patients (apart from those stabilised on another therapy with the treatment interval having been extended out to

more than 8 to 12 weeks). The other clinician stated that he would switch patients who were receiving injections every 1 to 2 months with the expectation that with longer durability the treatment interval could be extended over time.

- With respect to re-loading doses for patients who were switched, one clinician suggested that he would reload patients with 3 doses, with the exception being that patients whose treatment interval had already been extended out to 8 to 10 weeks might be reloaded with only 1 or 2 doses with the aim of extending the treatment interval quite quickly. The other clinician stated that following switching they would reload all patients with 3 doses, on the basis that pivotal trial data has shown that when a patient receives loading doses at the start that this leads to an optimum response.

The PBAC considered that the hearing was informative as it provided a clinical perspective on the challenges of treating this disease, the treatment burden on patients and the likely use of aflibercept 8 mg in clinical practice.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (8) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treating patients with aflibercept 8 mg including reduced treatment burden and hospital visits, and the potential for improved quality of life associated with a lower injection frequency.

6.3 The PBAC noted the advice received from the Macular Disease Foundation Australia clarifying the likely use of aflibercept 8 mg in clinical practice. The PBAC specifically noted the Foundation's comments that the use of aflibercept 8 mg may lead to a reduction in injection frequency, which could reduce treatment burden and out of pocket costs for patients, as well as improve longer term persistence, which in turn could reduce the risk of severe vision loss and blindness that can occur when treatment is stopped against the advice of the treating ophthalmologist. The comments from the Foundation suggested that this could be particularly important for patients living in rural and remote communities where access to ophthalmology providers is limited.

Clinical trial

6.4 The submission was based on one ongoing randomised head-to-head non-inferiority trial (PULSAR) comparing aflibercept 8 mg every 12 weeks (8q12) and aflibercept 8 mg every 16 weeks (8q16) with aflibercept 2 mg every 8 weeks (2q8) (n=1,011).

6.5 A phase 2, single-masked trial (CANDELA) comparing aflibercept 2 mg administered at 12-week intervals (2q12) with aflibercept 8q12 was presented as supportive evidence in an appendix to the submission. Given CANDELA 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. While exclusion of CANDELA was reasonable, its results were consistent with those observed in PULSAR trial.

6.6 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
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, p22 of the submission.

6.7 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Aflibercept 8 mg versus aflibercept 2 mg					
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, p26 of the submission.

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 60.

6.8 The PULSAR trial recruited men and women aged 50 years and older with active subfoveal CNV secondary to AMD, and excluded patients if they had prior therapy for nAMD or prior/concomitant ocular treatment of the study eye. The applicability of the PULSAR trial to the proposed PBS population is uncertain given that based on the proposed restrictions, patients with prior treatment may be prescribed aflibercept 8 mg.

6.9 The results in treatment-naive patients may not be generalisable to the targeted Australian population given that treatment-naive patients do not represent the complexity of disease and residual side effects that can be seen in treatment-experienced patients. The impact on comparative effectiveness and safety is unknown. Further, treatment-experienced patients who are switched from aflibercept 2 mg every 3 or 4 months to aflibercept 8 mg will have to receive the dose-loading regime (3 injections in the first 3 months), followed by T&E protocols to reach the stabilised dosing of one injection every 4 or 5 months. This increase in the number of injections for patients switching treatment may increase adverse events in clinical practice; the PBAC have previously considered that adverse events for anti-VEGF therapies in clinical practice are likely to be dependent on the frequency of administration (paragraph 7.6, faricimab nAMD Public Summary Document (PSD), May 2022 PBAC meeting).

6.10 In PULSAR, aflibercept 2 mg was dosed on a fixed 8-weekly schedule, with no provision for dose regimen modifications. This was not consistent with clinical practice or the approved TGA PI, which allows for dose modifications based on a T&E regimen up to every 16 weeks. However, the mean number of injections of aflibercept 2 mg in PULSAR (estimated by the evaluation to be 13.95 for 2 years of treatment, see the economic analysis section), was similar to the number of doses, based on data from the DUSC Secretariat (dated September 2023), estimated by the submission (14.01 injections in 2 years, based on patients initiating treatment in 2020/2021).

6.11 Patients in the aflibercept 8 mg arm of PULSAR could extend dosing intervals in Year 2 only. This was inconsistent with the draft PI for aflibercept 8 mg provided with the submission where it was proposed that extension of treatment intervals could be considered after the initial loading doses. Additionally, in the aflibercept 8 mg treatment arm, treatment intervals in PULSAR could be extended up to 24 weeks, inconsistent with the draft PI that proposed that treatment intervals could be extended up to every 20 weeks based on response. (Following the evaluation, the sponsor agreed to accept a maximum treatment interval of 16 weeks based on the recommendation of the TGA Delegate.) Therefore, the evaluation stated that the mean number of aflibercept 8 mg injections in the first year of the PULSAR trial might

be higher than what would be observed in clinical practice and might be lower than what would be observed in clinical practice after Year 1.

6.12 The primary outcome in PULSAR was a change from baseline in best corrected visual acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at week-48. Non-inferiority was assessed by comparing the lower bound of the 95% confidence interval (CI) for the estimated treatment difference in BCVA (8q12 vs 2q8; 8q16 vs 2q8) using a non-inferiority margin of 4 letters. A non-inferiority margin of 4 letters has previously been accepted by the PBAC for the treatment of patients with subfoveal CNV (paragraph 6.11, brolucizumab PSD, November 2019 PBAC meeting and paragraph 7.5, faricimab nAMD PSD, May 2022 PBAC meeting).

Comparative effectiveness

6.13 The results from PULSAR for the primary outcome, change from baseline in BCVA at week 48 and the secondary outcome, change from baseline in BCVA at week 60 are summarised in Table 4 and

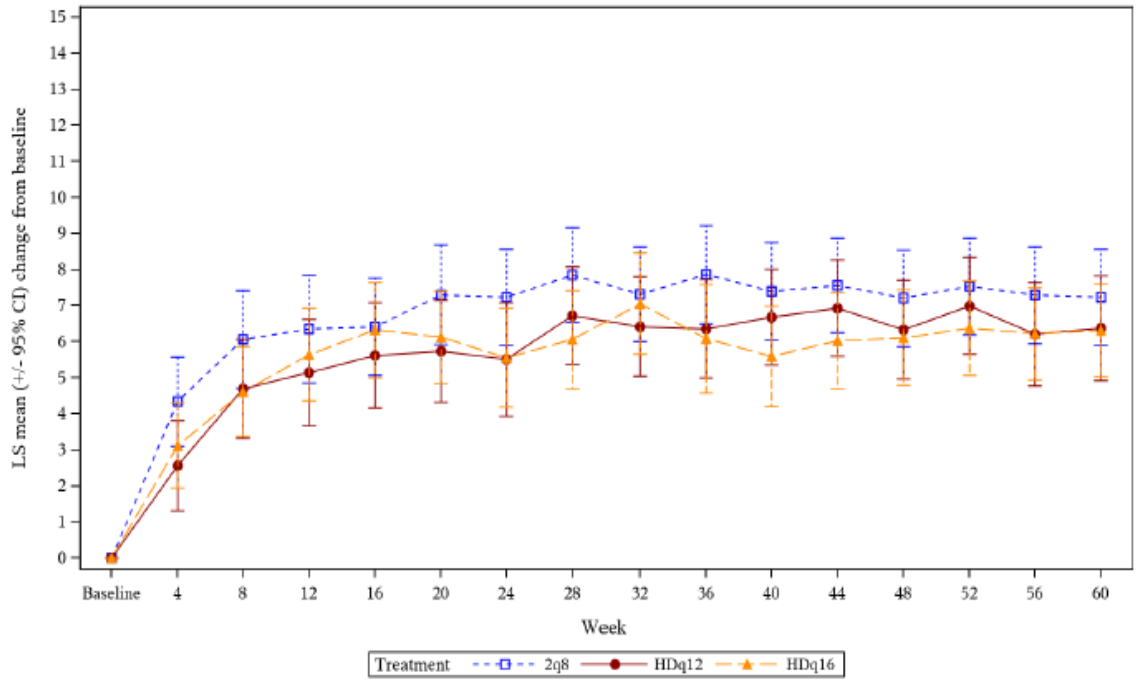
6.14 Figure 1. In all instances of comparison (at week 48 and 60 and between 2q8 versus 8q12 and 8q16), the 95% CI included 0, indicating treatment differences were not statistically significant. The p-values were statistically significant and the lower 95% confidence limits of the treatment differences were within the non-inferiority limit of 4 letters, thereby meeting the pre-specified non-inferiority margin.

Table 4: Results of BCVA in the PULSAR trial (FAS; MMRM)

	Aflibercept 8 mg		Aflibercept 2 mg	Estimate for contrast (95% CI)[a] Non-inferiority p-values[b]	
	8q12 (N=335)	8q16 (N=338)	2q8 (N=336)		
Mean baseline BCVA (ETDRS letter score)	59.9	60.0	58.9	**8q12 vs 2q8**	**8q16 vs 2q8**
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)		

Source: Table 2.17, p62 and Table 2.18, p65 of the submission.
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, 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 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
Bold indicates statistically significant results.

Figure 1: Least square mean change from baseline in BCVA score through week 60 (FAS; MMRM)



Source: Figure 2.8, p66 of the submission.
Abbreviations: 2q8= aflibercept 2 mg administered every 8 weeks, BCVA= best corrected visual acuity, FAS= full analysis set, HDq12= aflibercept 8 mg administered every 12 weeks, HDq16= aflibercept 8 mg administered every 16 weeks, LS= least squares; MMRM= mixed model for repeated measurements.

6.15 Results of the secondary outcome, mean National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ-25) is presented in Table 5. 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. The reduced number of injections observed in the aflibercept 8 mg treatment arm (6.9 injections in the 8q12 arm and 6.0 injections in the 8q16 arm at Week 60) compared to the aflibercept 2 mg treatment arm (8.5 injections at Week 60) did not translate into an improvement in quality of life as measured by the NEI-VFQ-25. However, this is not surprising noting that while the NEI-VFQ-25 contains 12 sub-scales, none of those subscales specifically refer to treatment administration.

Table 5: Change from baseline in NEI-VFQ-25 total score in the PULSAR trial (FAS; MMRM)

	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	Estimate for contrast (95% CI)[a] P-value	
Week 48					
Patients with data (%)	285 (85.1%)	266 (78.7%)	266 (79.2%)	–0.72	–0.87
Mean change from baseline (SD)	4.1 (10.4)	3.4 (10.8)	4.6 (11.0)	(–2.35, 0.90)	(–2.55, 0.80)
LS mean change from baseline (SE)	3.50 (0.70)	3.35 (0.72)	4.22 (0.70)	0.3817	0.3070
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		

Source: Table 2.25, p74 of the submission.

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.

[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 8q12 minus 2q8 and 8q16 minus 2q8, respectively with 2-sided 95% CIs

6.16 The population included in the PULSAR trial was younger (mean; 74-75 years) compared with the Australian population (mean; 79 years) described in the DUSC report, May 2018, of ranibizumab and aflibercept utilisation. Results of sub-group analyses conducted by the submission did not show any evidence of significant treatment effect modification.

Comparative harms

6.17 The incidence of adverse events and treatment-emergent adverse events (TEAEs) was comparable between treatment arms in the PULSAR trial. No significant treatment differences for study drug-related TEAEs IVT injection procedure related TEAEs, procedure related TEAEs or serious TEAEs were observed among treatment arms in the PULSAR study (Table 6). There were more vitreous floaters reported in the 2q8 treatment arm compared to the 8q12 treatment arm (13/336 [4.14%] versus 4/335 [1.19%] respectively; OR= 0.30 [95% IC, 0.10 to 0.93]). There were 10 deaths reported in the study and none were considered related to study drug by the investigator. Ocular TEAEs in the study eye were the cause of discontinuation of study drug in 4 (1.19%) participants in the 8q12 arm, 4 participants (1.18%) in the 8q16 arm, and 2 participants (0.6%) in the 2q8 arm.

Table 6: Summary of adverse events in the PULSAR trial though week 60 (SAF)

Treatment arm	8q12 (N=355) n/N (%)	8q16 (N=338) n/N (%)	2q8 (N=336) n/N (%)	8q12 vs 2q8		8q16 vs 2q8	
				OR (95% CI)	RD (95% CI)	OR (95% CI)	RD (95% CI)
Any AE	258/335 (77.01%)	278/338 (82.25%)	263/336 (78.27%)	0.93 (0.65, 1.34)	-0.01 (-0.08, 0.05)	1.29 (0.88, 1.88)	0.04 (-0.02, 0.10)
Any study drug-related TEAE	20/335 (5.97%)	15/338 (4.44%)	18/336 (5.36%)	1.12 (0.58, 2.16)	0.01 (-0.03, 0.04)	0.82 (0.41, 1.66)	-0.01 (-0.04, 0.02)
Any ocular TEAE	18/335 (5.37%)	13/338 (3.85%)	13/336 (3.87%)	1.41 (0.68, 2.93)	0.02 (-0.02, 0.05)	0.99 (0.45, 2.18)	-0.00 (-0.03, 0.03)
Any TEAE leading to discontinuation	5/335 (1.49%)	6/338 (1.78%)	8/336 (2.38%)	0.62 (0.20, 1.92)	-0.01 (-0.03, 0.01)	0.74 (0.25, 2.16)	-0.01 (-0.03, 0.02)
Any ocular TEAE	4/335 (1.19%)	4/338 (1.18%)	2/336 (0.60%)	2.02 (0.37, 11.09)	0.01 (-0.01, 0.02)	2.00 (0.36, 10.99)	0.01 (-0.01, 0.02)
Any non-ocular TEAE	1/335 (0.30%)	2/338 (0.59%)	6/336 (1.79%)	0.16 (0.02, 1.38)	-0.01 (-0.03, 0.00)	0.33 (0.07, 1.63)	-0.01 (-0.03, 0.00)
Serious adverse events							
Any SAE	52/335 (15.52%)	50/338 (14.79%)	61/336 (18.15%)	0.83 (0.55, 1.24)	-0.03 (-0.08, 0.03)	0.78 (0.52, 1.18)	-0.03 (-0.09, 0.02)
Any ocular serious TEAE	8/335 (2.39%)	8/338 (2.37%)	6/336 (1.79%)	1.35 (0.46, 3.92)	0.01 (-0.02, 0.03)	1.33 (0.46, 3.89)	0.01 (-0.02, 0.03)
Study eye	7/335 (2.09%)	7/338 (2.07%)	4/336 (1.19%)	1.77 (0.51, 6.11)	0.01 (-0.01, 0.03)	1.76 (0.51, 6.05)	0.01 (-0.01, 0.03)
Any TEAE	256/335 (76.42%)	273/338 (80.77%)	260/336 (77.38%)	0.95 (0.66, 1.36)	-0.01 (-0.07, 0.05)	1.23 (0.85, 1.78)	0.03 (-0.03, 0.10)
Any serious TEAE related to IVT injection procedure	2/335 (0.60%)	2/338 (0.59%)	2/336 (0.60%)	1.00 (0.14, 7.16)	0.00 (-0.01, 0.01)	0.99 (0.14, 7.10)	-0.00 (-0.01, 0.01)
Death and treatment-emergent events							
Any AE with outcome death	3/335 (0.90%)	2/338 (0.59%)	5/336 (1.49%)	0.60 (0.14, 2.52)	-0.01 (-0.02, 0.01)	0.39 (0.08, 2.05)	-0.01 (-0.02, 0.01)
Any TEAE of intraocular inflammation in study eye	4/335 (1.19%)	1/338 (0.30%)	4/336 (1.19%)	1.00 (0.25, 4.04)	0.00 (-0.02, 0.02)	0.25 (0.03, 2.22)	-0.01 (-0.02, 0.00)
Any adjudicated treatment-emergent ATEs[a]	1/335 (0.30%)	2/338 (0.59%)	8/336 (2.38%)	**0.12 (0.02, 0.99)**	**-0.02 (-0.04, -0.00)**	0.24 (0.05, 1.16)	-0.02 (-0.04, 0.00)
Any TEAE of hypertension	23/335 (6.87%)	22/338 (6.51%)	16/336 (4.76%)	1.47 (0.76, 2.84)	0.02 (-0.01, 0.06)	1.39 (0.72, 2.70)	0.02 (-0.02, 0.05)

Source: Table 2.26, p76 of the submission.

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, ATE = arterial thromboembolic events, 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.

Notes: OR and RD (and associated 95%CI) calculated post-hoc using Review Manager version 5.4

TEAEs are defined as AEs that started in the time frame 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.

[a] Arterial thromboembolic events were adjudicated by the Anti-Platelet Trialists' Collaboration.

Bold indicates statistically significant results.

Benefits/harms

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

Clinical claim

6.19 The submission described aflibercept 8 mg as non-inferior in terms of effectiveness compared to aflibercept 2 mg. This claim was adequately supported. The key issue was the applicability of the PULSAR trial to the proposed PBS population, specifically; the treatment schedule of aflibercept 8 mg during the first year did not align with the proposed PI and patients starting treatment in Australia can be treatment-experienced.

6.20 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable and was adequately supported by the data.

6.21 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.22 The submission presented a CMA comparing aflibercept 8 mg to aflibercept 2 mg based on the PULSAR trial.

6.23 The submission presented the CMA over a 2-year time horizon to account for induction dosing in the first year. This was reasonable given that a 2-year time horizon has previously been accepted by the PBAC for the same indication (paragraph 7.2, faricimab nAMD PSD, May 2022 PBAC meeting).

6.24 The key components and assumptions of the CMA are presented in Table 7.

Table 7: Summary of model structure, key inputs and rationale

Component	Assumption
Therapeutic claim: effectiveness	Based on the clinical evidence presented, effectiveness of aflibercept 8 mg is assumed to be non-inferior to aflibercept 2 mg
Therapeutic claim: safety	Based on the clinical evidence presented, safety of aflibercept 8 mg is assumed to be non-inferior to aflibercept 2 mg
Evidence base	Efficacy was informed by a direct comparison of aflibercept 8 mg and aflibercept 2 mg from the PULSAR trial. Drug utilisation was informed by PULSAR for aflibercept 8 mg and in-market (data provided by the DUSC Secretariat) for aflibercept 2 mg.
Equi-effective doses	Year 1: 6.17 doses of aflibercept 8 mg annually to 7.89 doses of aflibercept 2 mg annually Year 2: 3.94 doses of aflibercept 8 mg annually to 6.12 doses of aflibercept 2 mg annually
Direct medicine costs	Direct medicine costs of aflibercept 8 mg over 2 years was $[redacted], higher than the cost of aflibercept 2 mg over 2 years which was $[redacted]
Other costs or cost offsets	The costs associated with the administration procedure (funded under MBS item 42738) is expected to be less for aflibercept 8 mg compared with aflibercept 2 mg as ongoing aflibercept 8 mg injections are expected to be 35% less during the maintenance phase.

Source: Table 3-2, p107 of the submission.

6.25 The equi-effective dose for aflibercept 8 mg was estimated from the combined q12 and q16 arms of the PULSAR trial; and separately for the first and second year to account for the difference in dosing frequency as outlined in the proposed PI.

6.26 The equi-effective number of doses of aflibercept 8 mg in Year 1 was estimated as 6.17 injections, calculated as the mean active injections at 48 weeks divided by the mean treatment duration at 48 weeks, apportioned to a 52-week estimate. The ESC considered this assumption may be conservative against aflibercept 8 mg. That is, the data from PULSAR are likely to reflect more doses in Year 1 than would be observed in clinical practice given that the dosing regimen in PULSAR did not allow extensions in the treatment interval in Year 1 compared to the dosing regimen proposed in the draft PI where the proposal was that the treatment interval may be extended after induction dosing, up to 20 weeks. Based on the TGA Delegate's overview, the maximum extension to the treatment interval was proposed to be 16 weeks.

6.27 The equi-effective number of doses of aflibercept 8 mg in Year 2 was estimated from the distribution of patients on each dosing interval at 96 weeks, as 3.94 injections. In estimating the equi-effective number of doses, patients on a 24-week dosing interval in PULSAR were pooled with patients on a 20-week dosing interval. Pooling of patients was appropriate given the draft PI provided with the submission stated that the dosing interval for aflibercept 8 mg may be extended up to a maximum of 20 weeks. The ESC noted that estimating the equi-effective number of doses of aflibercept 8 mg in Year 2 from the distribution of patients on each dosing interval at 48 weeks or 60 weeks resulted in a similar number of doses: 4.28 or 4.33 doses respectively.

6.28 The equi-effective number of doses of aflibercept 2 mg was 7.89 injections in Year 1 and 6.12 injections in Year 2 (14.01 doses for Years 1 and 2). The estimated mean number of doses was based on PBS data provided by the DUSC Secretariat instead of PULSAR trial data. Given the dose regimen of aflibercept 2 mg in the PULSAR trial was not representative of T&E regimens in Australian clinical practice this was reasonable. The mean number of doses calculated for aflibercept 2 mg was similar to those accepted by the PBAC in its consideration of faricimab (Year 1; 7.69 doses, Year 2; 6.31 doses) (paragraph 7.2, faricimab nAMD PSD, May 2022 PBAC meeting).

6.29 The approach adopted by the submission in its estimation of the equi-effective dose of aflibercept 2 mg included patients who discontinued aflibercept 2 mg in the PBS dataset. This was inconsistent with the PBAC Guidelines however, the inclusion of these patients decreased the mean number of aflibercept 2 mg doses, which resulted in a lower cost-minimised price. The ESC considered the submission's approach of including patients who discontinued to be conservative against aflibercept 8 mg.

6.30 Based on the data and relativities presented above, the submission concluded that 6.17 doses of aflibercept 8 mg annually and 7.89 doses of aflibercept 2 mg annually are equi-effective for Year 1 and 3.94 doses of aflibercept 8 mg annually and 6.12 doses of aflibercept 2 mg annually are equi-effective for Year 2.

6.31 The submission included cost offsets associated with differences in the frequency of administering aflibercept 8 mg and 2 mg in the CMA. The submission did not include the cost of monitoring for both treatments. Exclusion of monitoring costs such as optical coherence tomography or fluorescein angiography used in assessing the improvement of visual acuity was conservative against aflibercept 8 mg as it resulted in a lower price. The ESC considered the exclusion of monitoring costs may be conservative against aflibercept 8 mg.

6.32 The results of the CMA are presented in Table 8 and are based on the proposed effective prices.

Table 8: Summary: Results of the cost-minimisation approach (as proposed in the submission)

Component	Aflibercept 8 mg	Aflibercept 2 mg
Treatment cost		
Aflibercept 8 mg cost per administration (AEMP)	$	
Aflibercept 8 mg frequency of administration over two-years	10.10	
Total cost of aflibercept 8 mg	$	
Aflibercept 2 mg cost per administration (AEMP)		$
Aflibercept 2 mg frequency of administration over two-years		14.01
Total cost of aflibercept 2 mg		$
Administration cost		
Unit cost per administration (MBS item: 42738)	$331.05	
Total administration cost	$3,345.07	$4,638.01
Total cost of drug over 2 years	$	$

Source: Table 3-7, p116 of the submission.
Abbreviations: AEMP = approved ex-manufacturer price, MBS = Medicare benefit schedule.
Note: the AEMP cost of aflibercept 8 mg was estimated as: (total cost of drug over 2 years – total administration cost)/administration frequency over 2 years.
Amended during the evaluation using the updated MBS scheduled fee for intravitreal injection (MBS item 42738) which was updated on 1 November 2023 (updated from $329.40 as used in the submission to $331.05). The overall impact on the estimation was negligible (recalculated effective AEMP; $ vs. submission's estimate; $).

6.33 The equi-effective dose of aflibercept 2 mg was based on utilisation data provided by the DUSC Secretariat for aflibercept 2 mg/ranibizumab. Applying the same approach utilised by the submission in calculating the mean number of doses of aflibercept 8 mg in Year 1, the evaluation estimated the mean number of doses of aflibercept 2 mg for the 2-year time horizon in PULSAR to be 13.95 (mean number of active injections of aflibercept 2 mg at 96 weeks (11.93) adjusted for treatment duration at 96 weeks (88.91) and apportioned to 104 weeks). Applying this trial-based mean number of doses for aflibercept 2 mg, the change in the cost-minimised price for aflibercept 8 mg was negligible (-0.6% ($-)).

6.34 The cost-minimised price estimated for aflibercept 8 mg will depend on the realisation in clinical practice of the applied dose frequencies for aflibercept 8 mg, derived from PULSAR. The Pre-Sub-Committee Response (PSCR) and the pre-PBAC response stated that the dosing frequency of aflibercept 8 mg in clinical practice is more likely to be lower, rather than higher, than the dosing frequency observed in the PULSAR clinical trial and implemented in the cost-minimisation.

6.35 The cost-minimisation implicitly assumes that patients treated with less frequent doses of aflibercept 2 mg will have the same health outcomes as patients in PULSAR

who were treated more frequently. Taken together, this means the cost-minimisation approach used a dosing frequency for aflibercept 8 mg that is based on proven clinical outcomes versus a lower dosing frequency for aflibercept 2 mg that is potentially – but admittedly unlikely – associated with inferior health outcomes. The ESC noted the maximum time between doses of aflibercept 8 mg in PULSAR (24 weeks) was longer than that recommended in the proposed Product Information and considered that this may lead to a higher number of injections in clinical practice than in the clinical trial. However, the ESC noted that the cost-minimisation had accounted for this in the equi-effective dose calculation by assuming all patients dosed at intervals of 20 or 24-weeks in PULSAR would be dosed at an interval of 20 weeks. The PBAC noted the maximum recommended time between doses had been reduced to 16 weeks in the TGA Delegate's Overview and that the impact of this on the cost-minimised price had been estimated in the sponsor's pre-PBAC response (see Table 9).The ESC noted that the cost-minimised price estimated for aflibercept 8 mg will depend on compliance to the proposed longer dosing intervals compared to a shorter dosing interval for aflibercept 2 mg in clinical practice. Moreover, the ESC considered that, while the equi-effective doses proposed were appropriate for treatment naïve (incident) patients commencing aflibercept 8 mg or 2 mg accordingly, they were not appropriate for patients currently on VEGF-I treatment (prevalent) patients. These prevalent patients would be expected to continue their current regimen and not require the loading dose and so would be expected to have the same number of aflibercept 2 mg injections in Year 1 as in Year 2 (i.e., 6.12 injections/year in Year 1 and 2). The ESC considered the cost-minimised price should be weighted to account for prevalent patients who switch to aflibercept 8 mg. The pre-PBAC response stated that "the ESC methodology is also inconsistent with what was accepted by the PBAC in the faricimab submission where the higher number of doses in switching patients would have been a similar concern but ultimately was not accounted for in the cost-minimisation analysis accepted by the PBAC".

6.36 Following receipt of the TGA Delegate's Overview, which stated: "the sponsor has agreed to change the proposed PI dosing instructions, and a 16-week interval is now the maximum in line with the pivotal trial data", the pre-PBAC response presented a revised cost-minimisation based on a maximum treatment interval of 16 weeks (see Table 9 below). This revised analysis was presented using 96-week data from PULSAR, assuming that all patients were treatment naïve (incident patients) and making no allowance for re-loading doses.

Table 9: Summary: **Results of the cost-minimisation approach – REVISED**

Component	Aflibercept 8 mg	Aflibercept 2 mg
Treatment cost		
Aflibercept 8 mg cost per administration (AEMP)	$ (previously $)	
Aflibercept 8 mg frequency of administration over 2 years	10.39* (previously 10.10)	
Total cost of aflibercept 8 mg	$	
Aflibercept 2 mg cost per administration (AEMP)		$
Aflibercept 2 mg frequency of administration over 2 years		14.01
Total cost of aflibercept 2 mg		$
Administration cost		
Unit cost per administration (MBS item: 42738)	$331.05	
Total administration cost	$3,438.08	$4,638.01
Total cost of drug over 2 years	$	$

Source: pre-PBAC response

* 6.17 injections in the 1st year PLUS 4.22 injections in the 2nd year.

6.37 In their pre-PBAC response the sponsor stated they intend to submit to the TGA to change the maximum dosing interval out to 20 weeks, based on the 96-week data from the Clinical Study Report from PULSAR.

6.38 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with aflibercept 8 mg would be no more than the cost per patient of aflibercept 2 mg. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this case, the PBAC should consider the following parameters: frequency of administering aflibercept 8 mg and aflibercept 2 mg in clinical practice, and the impact of additional loading doses being required for patients switching from aflibercept 2 mg to aflibercept 8 mg.

Drug cost/patient/year

6.39 The drug cost per patient per year is presented in Table using the effective prices of aflibercept 8 mg and aflibercept 2 mg.

6.40 The reduced administration cost for aflibercept 8 mg due to the reduced administration frequency results in an additional annual drug cost of $ per patient averaged over the first 2 years.

Table 10: Drug cost per patient per year for proposed and comparator drugs (using prices updated in pre-PBAC response)

	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	$			$		
Cost/patient/year	$	$	$	$	$	$

Source: constructed during the evaluation.

Abbreviations: CMA= cost-minimisation approach

[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

6.41 This submission was not considered by DUSC. The submission used a market share approach to estimate the extent of use and financial impact of listing aflibercept 8 mg on the PBS. The market size of anti-VEGF therapies for nAMD was estimated from the historical use of aflibercept 2 mg and ranibizumab for nAMD. The sources of data utilised are shown in

6.42 Table 9.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Anti-VEGF market without listing of aflibercept 8 mg		
Estimated anti-VEGF market for 2022 (scripts)	414,361. Based on Medicare statistics: estimated as the number of scripts for aflibercept 2 mg and ranibizumab for item numbers relevant to the nAMD indication.	
Annual market growth (in scripts)	14,000 in Year 1 decreasing to 12,500 in Year 6.	The market growth may be underestimated and the magnitude of any reduction in market growth depends on the uptake rate of faricimab, which remains uncertain. The % growth applied by the submission ranged from 3.27% in the first year to 2.53% in Year 6. The PSCR stated that while the overall anti-VEGF market is expected to grow that the rate of growth each year in terms of script usage would be expected to slightly decline since faricimab is expected to gain market share offering a more favourable script equivalence versus aflibercept 2 mg / ranibizumab.
Projected market size of the current anti-VEGF treatments	442,361 in Year 1 increasing to 507,361 in Year 6. Calculated 2022 scripts for anti-VEGF treatments and the assumed annual growth of anti-VEGF market	Refer to comment above.
Distribution of treatment type (initiation and continuation) in the current market	10%/90% split for initiation/continuation for the 6 years period for aflibercept 2 mg and ranibizumab. 26%/74% split for Year 1 and 14%/84% split for subsequent years per initiation/continuation for faricimab Observed historical utilisation trend of ranibizumab and aflibercept 2 mg sourced from the DUSC report (May 2018).	The submission estimated the distribution of initiation and continuation scripts for faricimab by adjusting historical aflibercept/ranibizumab utilisation data for the script equivalence, i.e., using the dosing relativity between faricimab and aflibercept/ ranibizumab. This approach accounts for the differences in dosing between faricimab and aflibercept/ranibizumab.
Anti-VEGF market with the listing of aflibercept 8 mg		

Parameter	Value applied and source	Comment
Uptake rate, by total treatment	No direct substitution was assumed for ranibizumab Aflibercept 8 mg would substitute for [redacted]% of aflibercept 2 mg and faricimab scripts in Year 1, increasing to [redacted]% of aflibercept 2 mg scripts and [redacted]% of faricimab scripts in Year 6. Assumed uptake rates for Year 1 and Year 6 and estimated values for Year 2 to Year 5 as a constant growth of change based on the assumed values	The assumed 0% substitution of ranibizumab was reasonable given the observed decline in its use. It appeared the substitution rate assumed in Year 1 for both aflibercept 2 mg and faricimab was based on the observed historical (Year 2017) initiation scripts for aflibercept 2 mg and ranibizumab presented in the DUSC report (May 2018). The ESC considered that the uptake of aflibercept 8 mg and substitution of other VEGF-I including aflibercept 2 mg and faricimab was uncertain.
Uptake rate, by treatment distribution (initiating/continuing split)	Observed historical utilisation trend of ranibizumab and aflibercept 2 mg sourced from DUSC report (May 2018) and faricimab nAMD PSD, May 2022	The same approach used for the anti-VEGF market without aflibercept 8 mg above.
Script equivalence	Aflibercept 2 mg Initial scripts: 1:1; Continuing scripts: 0.69; Continuing scripts to initial scripts: 1.96 Faricimab Initial scripts: 1:1; Continuing scripts: 0.98; Continuing scripts to initial scripts: 2.79	Using equi-effective dose proposed in pre-PBAC response and information from faricimab PSD (May 2022 PBAC meeting). The PBAC noted the financial estimates assumed there would be fewer continuing aflibercept 8 mg scripts relative to faricimab even though the maximum dosing interval is the same (16 weeks).
Costs		
Aflibercept 8 mg	Effective price DPMQ: $[redacted] EMP: $[redacted]	Effective price proposed in pre-PBAC response
Aflibercept 2 mg	Effective price DPMQ: $[redacted] EMP: $[redacted]	
Faricimab	Assumed effective price: DPMQ: $[redacted] EMP: $[redacted]	
Patient copayment	PBS: $11.35 RPBS: $7.12 Based on current use of aflibercept 2 mg and faricimab.	
MBS costs	$331.05 MBS item 42738	Cost was updated during evaluation

Source: Table 4-1, p118, Table 4-5, p122, Table 4-7 and Table 4-8, p123, Table 4-8 and Table 4-9, p124, Table 4-10, p125, Table 4-11 and Table 4-12, p126, Table 4-13, p127 and Table 4-17, p130 of the submission.
Abbreviations: DPMQ = dispensed price for maximum quantity, DUSC = Drug Utilisation Sub Committee, EMP = ex-manufacturer price, MBS = Medical Benefit Scheme, mg = milligram, PBAC = Pharmaceutical Benefit Advisory Committee, PBS = Pharmaceutical Benefit Scheme; PSD = Public Summary Document, RPBS = Repatriation Pharmaceutical Benefit Scheme; VEGF = Vascular Endothelial Growth Factor.

6.43 The submission relied on a number of assumptions to derive the substitution of aflibercept 8 mg from aflibercept 2 mg and faricimab. While the evaluation considered that the assumptions used by the submission to derive the expected utilisation of aflibercept 8 mg were generally reasonable, the evaluation and the ESC considered

the estimates were uncertain given the complex approach and number of assumptions used to estimate the utilisation of aflibercept 8 mg. Overall, the submission predicted that the introduction of aflibercept 8 mg into the current nAMD market will result in 40% of all nAMD patients receiving aflibercept 8 mg for PBS-subsidised anti-VEGF maintenance treatment in Year 6 of its listing.

6.44 The estimated utilisation and financial impact of listing aflibercept 8 mg on the PBS using the effective price for aflibercept 8 mg and aflibercept 2 mg and the assumed effective price for faricimab and adjusted for a maximum treatment interval for aflibercept 8 mg of 16 weeks, is presented in Table 12.

Table 10: Estimated use and financial implications (Effective price for aflibercept 8 mg and 2 mg and assumed effective price for faricimab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of aflibercept 8 mg						
Number of scripts dispensed	[1]	[2]	[3]	[4]	[4]	[4]
Estimated financial implications of aflibercept 8 mg						
Cost to PBS/RPBS less copayments	[5]	[10]	[6]	[7]	[8]	[8]
Estimated financial implications for aflibercept 2 mg and faricimab						
Cost to PBS/RPBS less copayments	[9]	[9]	[9]	[9]	[9]	[9]
Net financial implications						
Net cost to PBS/RPBS	[11]	[12]	[12]	[12]	[12]	[12]
Net cost to MBS	[9]	[9]	[9]	[9]	[9]	[9]
Net cost to Government	[11]	[11]	[11]	[11]	[11]	[11]

Source: Table 11, pre-PBAC response, assuming 85% MBS benefit

The redacted values correspond to the following ranges:

[1] *30,000 to < 40,000*
[2] *50,000 to < 60,000*
[3] *80,000 to < 90,000*
[4] *100,000 to < 200,000*
[5] *$20 million to < $30 million*
[6] *$60 million to < $70 million*
[7] *$80 million to < $90 million*
[8] *$100 million to < $200 million*
[9] *net cost saving*
[10] *$40 million to < $50 million*
[11] *$0 to < $10 million*
[12] *$10 million to < $20 million*

6.45 The total cost to the PBS/RPBS of listing aflibercept 8 mg was estimated to be $20 million to < $30 million in Year 1 and $400 million to < $500 million over the first 6 years of listing. This was associated with a net cost to the PBS/RPBS, after accounting for substitution for aflibercept 2 mg and faricimab, of $0 to < $10 million in Year 1 and $70 million to < $80 million over the first 6 years of listing.

6.46 The pre-PBAC response acknowledged the cost implications of the re-loading doses but noted that as substitution is likely to be skewed towards patients receiving injections of aflibercept 2 mg who currently have relatively short injection intervals, that the substitution-related cost offsets from aflibercept 2 mg would be greater than presented in the submission.

6.47 The total cost to the PBS/RPBS was partially offset by a reduction of MBS costs associated with reduced IVT injection administration frequency. The total net cost to the government of listing aflibercept 8 mg was estimated to be $0 to < $10 million in Year 1 and $30 million to < $40 million over the first 6 years of listing.

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 for the treatment of patients with visual impairment caused by subfoveal choroidal neovascularisation secondary to age-related macular degeneration (nAMD). The PBAC's recommendation for listing was based on, among other matters, its assessment 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.

7.2 The PBAC welcomed comments received from health care professionals, and the Macular Disease Foundation Australia, via the Consumer Comments facility on the PBS website. The PBAC noted that a common theme raised in the comments was that a lower injection frequency is likely to reduce the burden of access to treatment, and this was also highlighted by clinicians during the sponsor hearing. The PBAC also noted that faricimab is available on the PBS and that dosing can be extended up to every 16 weeks, the same as for aflibercept 8 mg.

7.3 The PBAC noted the input from the clinicians at the sponsor hearing suggested that most patients switched from their current anti-VEGF treatment to aflibercept 8 mg would receive re-loading doses.

7.4 The PBAC considered the nominated comparator of aflibercept 2 mg was appropriate and noted that aflibercept 2 mg, faricimab and ranibizumab were all alternative therapies as they could be replaced in clinical practice. The PBAC noted that no evidence was provided to demonstrate aflibercept 8 mg provided a significant improvement in efficacy and/or reduction of toxicity over the alternative therapies.

7.5 The PBAC noted the clinical claim of non-inferior efficacy and safety was based on the evidence presented in the PULSAR non-inferiority trial that compared aflibercept 8 and aflibercept 2 mg. The Committee noted that the trial protocol restricted patients such that: (i) treatment intervals could be extended (up to 24 weeks) from Week 52 for patients treated with aflibercept 8 mg, and (ii) treatment intervals could not be extended for patients treated with aflibercept 2 mg. The PBAC noted this was not consistent with clinical practice. as both agents could use a treat and extend (T&E) approach following loading doses (3 monthly injections for aflibercept 8 mg and aflibercept 2 mg). Additionally, the PBAC noted the treatment interval for aflibercept 8 mg could be extended to 24 weeks (based on response) which is not consistent with the draft Product Information, where the maximum recommended treatment interval will be 16 weeks (agreed to by the sponsor).

7.6 The PBAC considered the claim of non-inferior comparative efficacy to be adequately supported, noting that the pre-specified non-inferiority margin of 4 letters was met for the primary endpoint of change in best corrected visual acuity (BCVA) score from baseline between the treatment groups.

7.7 The PBAC noted the incidence of adverse events and treatment-emergent adverse events was comparable between the treatment groups in PULSAR and considered the claim of non-inferior comparative safety for aflibercept 8 mg and aflibercept 2 mg was reasonable.

7.8 The PBAC considered the cost-effectiveness of aflibercept 8 mg would be acceptable if it were cost-minimised (over 2 years) to the lowest cost alternative treatment for the same indication.

7.9 The PBAC noted the trial dosing intervals in the PULSAR trial were not consistent with clinical practice (as discussed in paragraphs 6.10 and 6.11). The PBAC noted the equi-effective doses proposed in the pre-PBAC response used trial data for aflibercept 8 mg (adjusted for a maximum 16-week treatment interval) and utilisation data provided by the DUSC Secretariat for aflibercept 2 mg. The PBAC noted the pre-PBAC response proposed that 10.39 injections of aflibercept 8 mg (6.17 injections in Year 1, 4.22 injections in Year 2) were equi-effective to 14.01 injections of aflibercept 2 mg (7.89 injections in Year 1, 6.12 injections in Year 2). The PBAC considered the equi-effective doses were uncertain.

7.10 The PBAC noted the maximum treatment interval for faricimab was also 16 weeks and therefore considered it was reasonable to use a 1:1 dosing relativity for aflibercept 8 mg: faricimab. The PBAC acknowledged aflibercept 8 mg required one less loading dose initially but considered that, on balance, a 1:1 dosing relativity was reasonable. The PBAC noted the dosing relativity previously accepted for aflibercept 2 mg: ranibizumab was 1:1.

7.11 The PBAC noted the proposed equi-effective doses for aflibercept 8 mg and aflibercept 2 mg proposed in the pre-PBAC response (10.39 vs 14.01 doses, respectively) were more favourable for aflibercept 8 mg than the previously determined equi-effective doses for faricimab and aflibercept 2 mg (11.50 vs 14.00 doses, respectively). Noting the uncertainty with the proposed equi-effective doses, and 1:1 relativity vs faricimab (as per paragraph 7.10), the PBAC considered there was insufficient evidence to support more favourable equi-effective doses for aflibercept 8 mg and therefore the equi-effective doses should be the same as previously accepted for faricimab. On this basis, the PBAC advised the equi-effective doses over 2 years 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

7.12 The PBAC considered the financial estimates had appropriately been prepared based on a market share approach. The PBAC noted the financial estimates provided in the pre-PBAC response (see Table 10) resulted in a net cost to the PBS/RPBS over the first 6 years of listing. The PBAC noted this was in part due to:

(i) the drug cost for aflibercept 8 mg is higher than the drug cost for aflibercept 2 mg as the CMA accounts for the cost of administration;

(ii) prevalent treated patients switching to aflibercept 8 mg incur additional costs due to loading doses (which were not accounted for in the CMA). This impact is largely in the first two years of listing.

7.13 However, the PBAC noted that, based on a CMA versus the lowest cost alternative using the equi-effective doses outlined in paragraph 7.11 there was likely to be a saving to the PBS/RPBS over the first 6 years of listing of aflibercept 8 mg.

7.14 The PBAC considered the requested listing was appropriate, noting it was consistent with the current listings for the other VEGF inhibitors. The PBAC considered that a grandfather restriction should be in operation for a maximum of 12 months from listing and that the following administrative note should be added “Patients may qualify for PBS-subsidised treatment under this restriction once only per eye. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.”

7.15 The PBAC advised that aflibercept 8 mg is not suitable for prescribing by nurse practitioners.

7.16 The PBAC recommended that the Early Supply Rule should not apply.

7.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because aflibercept 8 mg 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 2009* for Pricing Pathway A were not met.

7.18 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	№.of Rpts	Available brands
AFLIBERCEPT					
Initial and Grandfather treatment					
aflibercept 8 mg/0.07 mL injection, 0.07 mL vial	NEW	1	1	2	Eylea
Continuing treatment					
aflibercept 8 mg/0.07 mL injection, 0.07 mL vial	NEW	1	1	2	Eylea
Restriction Summary edit 13343 / Treatment of Concept: edit 13424					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒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.					
Indication: Subfoveal choroidal neovascularisation (CNV)					
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) 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.
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 edit 13383 / Treatment of Concept: edit 13406
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒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
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 13343 / Treatment of Concept: edit 13424
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners

☒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) 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.
Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
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.
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

This restriction 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.