5.01 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 an Authority Required, General Schedule listing of aflibercept 8 mg for the treatment of patients with visual impairment due to diabetic macular oedema (DMO). The key components of the submission are summarised in Table 1.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus aflibercept 2 mg.

1.3 A submission for aflibercept 8 mg for the treatment of neovascular age-related macular degeneration (nAMD) was also considered at the May 2024 Pharmaceutical Benefits Advisory Committee (PBAC) meeting.

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

Component	Description
Population	Patients with visual impairment due to diabetic macular oedema (DMO)
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 DMO, aflibercept 8 mg is non-inferior in terms of efficacy and safety compared to aflibercept 2 mg

Source: Table 1-2 p5 of the submission

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 evaluation 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 diabetic macular oedema.

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

3 Requested listing

Name, restriction, manner of administration, form	Maximum Qty (packs)	Maximum Qty (units)	No. of repeats	DPMQ	Proprietary Name and Manufacturer
Initial and Continuation Aflibercept solution for intravitreal injection[a] 8 mg vial: 11.43 mg/ 0.1 mL, 0.1 mL vial 8 mg pre-filled syringe: 11.43 mg/ 0.1 mL, 0.1 mL syringe	1	1	5	$1,297.17 (published) $[redacted] (effective)	Eylea Bayer Australia Ltd

Category/Program	Section 85 – General Schedule
Prescriber type	Medical Practitioners
Indication	Diabetic macular oedema (DMO)
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 patient must have visual impairment due to diabetic macular oedema AND Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the Early Treatment Diabetic Retinopathy Study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment AND The condition must be diagnosed by optical coherence tomography; or The condition must be diagnosed by fluorescein angiography AND The treatment must be as monotherapy; or The treatment must be in combination with laser photocoagulation 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	Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye AND The treatment must be as monotherapy; or The treatment must be in combination with laser photocoagulation AND The treatment must be the sole PBS-subsidised therapy for this condition

Source: Table 1-6 p14, Table 1-7 p15 of the submission, Table 1-8 p16 of the submission,
DMO = diabetic macular oedema; DPMQ = dispensed price for maximum quantity; HPOS = Health Professional Online Services; PFS = pre-filled syringe; PBS = Pharmaceutical Benefits Schedule
[a] Each vial and PFS provides a usable amount to deliver a single dose of 70 microlitre solution for intravitreal injection containing aflibercept 8 mg. The DPMQ was updated during the evaluation (from $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 a published ex-manufacturer price for aflibercept 8 mg of $1,173.08 per injection and an effective ex-manufacturer price of $ (based on a cost-minimisation approach to aflibercept 2 mg).

3.2 The proposed restrictions are consistent with the current PBS restrictions for aflibercept 2 mg, ranibizumab and faricimab for DMO.

3.3 The proposed PBS listing includes restrictions based on the presence/level of visual impairment, method of diagnosis, and use of aflibercept as monotherapy or in combination with laser photocoagulation, making it narrower than the proposed TGA listing.

3.4 There were differences between the proposed restriction and the eligibility criteria for PHOTON (the pivotal study presented in the submission) with respect to patient's age, central retinal thickness (CRT), the level of visual impairment, use as monotherapy or in combination with laser photocoagulation and prior VEGF treatment.

3.5 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.

3.6 The submission requested grandfathering provisions for patients who initiate treatment with aflibercept 8 mg through an early access program planned for 2024, prior to PBS listing. The submission did not provide an estimate of the number of eligible grandfathered patients if aflibercept received a positive PBAC recommendation.

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

4 Population and disease

4.1 Diabetic retinopathy describes microvascular abnormalities on the interior surface of the eye (fundus) that develop in persons with diabetes. DMO is an advanced manifestation of diabetic retinopathy and is characterised by retinal thickening/swelling due to accumulation of fluid within the retina. DMO affects approximately 6.8% of the patient population with diabetes mellitus. Symptoms of macular oedema include blurring or distortion of central vision, and disturbance in the perception of colours. DMO causes visual impairment. If left untreated, the majority of patients lose more than two lines of visual acuity (VA) within two years. The burden of DMO on society is expected to increase with the increasing prevalence of diabetes mellitus.

4.2 The current standard of care for patients with DMO is intravitreal (IVT) administration of anti-VEGF therapy. Three anti-VEGF IVT therapies (aflibercept 2 mg, ranibizumab and faricimab) are currently listed on the PBS for the treatment of DMO. Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 (VEGF-R1) and 2 (VEGF-R2) extracellular domains fused to the Fc proportion of human immunoglobulin G (IgG) 1.

4.3 Aflibercept 2 mg is currently the most widely used IVT anti-VEGF therapy for DMO. The dosing regimen for aflibercept 2 mg is five initial monthly loading doses, followed by an 8-week dosing interval, with possible extension of that interval based on physician's assessment of visual and/or anatomic outcomes. 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.

4.4 The proposed dose for aflibercept in the 8 mg 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 (based on the TGA Delegate's Overview).

4.5 The submission positioned aflibercept 8 mg as an alternative to the PBS-listed anti-VEGF therapies ranibizumab, aflibercept 2 mg and faricimab.

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 commonly used anti-VEGF treatment for DMO on the PBS and is the therapy most likely to be replaced. This argument was supported by PBS dispensing data presented in the submission, which indicated that in 2022/23

aflibercept, ranibizumab and faricimab[1] accounted for 81%, 14% and 5% of PBS dispensed items for DMO, respectively.

- The PBAC has previously accepted claims of non-inferiority between aflibercept 2 mg and ranibizumab (paragraph 7.2, aflibercept DMO Public Summary Document (PSD), November 2014 PBAC Meeting) and between aflibercept 2 mg and faricimab (paragraph 7.3, faricimab DMO PSD, May 2022 PBAC meeting), and therefore aflibercept 2 mg can be considered representative of available anti-VEGF therapies.

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 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

[1] Listed on the PBS 1 January 2023

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.

6.2 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

6.3 The PBAC noted and welcomed the input from individuals (1), health care professionals (6) 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. The comments highlighted that there could be benefit over aflibercept 2 mg in Aboriginal and Torres Strait Islander people who are diabetic and in rural populations, where there may be reduced access to specialist ophthalmology services.

6.4 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 noted the Foundation's comments that the use of aflibercept 8 mg may lead to a reduction in injection frequency, which could help reduce anxiety associated with injections, reduce the burden on health professionals and carers, and improve longer term compliance and patient satisfaction. The comments from the Foundation suggested that this could be particularly important for Aboriginal and Torres Strait Islander people.

Clinical trial

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PHOTON (NCT04429503)	A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high dose aflibercept in patients with diabetic macular edema. VGFTe-8-DME-1934. Amendment 4	Clinical Study Protocol, April 2022
	A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high dose aflibercept in patients with diabetic macular edema	Clinical Study Report, January 2023
	A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high dose aflibercept in patients with diabetic macular edema. Amendment Version 2.0 / 19	Statistical analysis plan, August 2022
	Brown DM. Baseline Disease Characteristics of Patients Who Maintained 12- and 16-Week Aflibercept 8 mg Dosing Versus Patients with Shortened Treatment Intervals Through Week 48 in the Phase 2/3 PHOTON Trial.	Investigative Ophthalmology and Visual Science. 2023;64(8):2813
	Do DV. Aflibercept 8 mg for Diabetic Macular Edema: 48-Week Results From the Phase 2/3 PHOTON Trial.	Investigative Ophthalmology and Visual Science. 2023;64(8):2814
	Ghorayeb G. Intravitreal Aflibercept 8 mg for Diabetic Macular Edema: Week 48 Efficacy Outcomes by Baseline Demographics in the Phase 2/3 PHOTON Trial.	Investigative Ophthalmology and Visual Science. 2023;64(8):2707
	Schneider E. Pooled Safety Analysis of Aflibercept 8 mg in the CANDELA, PHOTON, and PULSAR Trials.	Investigative Ophthalmology and Visual Science. 2023;64(8):3724

Source: Table 2-3 p25 of the submission
DME = diabetic macular oedema; VEGF = Vascular endothelial growth factor

6.6 The submission was based on one head-to-head trial (PHOTON, N=660) comparing aflibercept 8 mg 12-weekly (8q12) or aflibercept 8 mg administered 16-weekly (8q16), to aflibercept 2 mg 8-weekly (2q8) injection intervals. The key features of PHOTON are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
PHOTON	660	R, MC, DB, non-inferiority Ongoing (96 weeks)	Low	• Adults with macular thickening secondary to DMO involving the centre of the fovea • BCVA ETDRS letter score of 78 to 24 in the study eye with decreased vision primarily because of DMO • Type 1 or 2 diabetes • CRT ≥300 µm (or ≥ 320 µm on Spectralis) as determined by the reading centre at the screening visit.	**Primary:** • Change in BCVA **Key secondary:** • Change in BCVA • ≥2-step improvement on the ETDRS DRS **Additional secondary**: • Proportion of patients gaining ≥15 letters in BCVA • Proportion of patients with BCVA ≥ 69 letters; • Change in CST • Proportion of patients with leakage on fluorescein angiography • Quality of life (NEI VFQ-25) • Adverse events

Source: Prepared during the evaluation based on Section 2.3 of the submission
BCVA = best corrected visual acuity; CST = central subfield thickness; CRT = Central retinal thickness; DB = double blind; DMO = diabetic macular oedema; DRS = diabetic retinopathy severity; ETDRS = Early Treatment Diabetic Retinopathy Study; MC = multi-centre; NEI VFQ-25 = National Eye Institute Visual Functioning Questionaire-25 ; R = randomised;

6.7 PHOTON is an ongoing, international, randomised non-inferiority trial. The submission was based on the results of the primary analysis for PHOTON, reported for a mean duration of follow-up of approximately 48 weeks. Treatment is planned to continue for a total of 96 weeks. Patients who complete PHOTON will be eligible to participate in an open-label extension study until Week 156.

6.8 PHOTON recruited adults with DMO involving the centre of the fovea. Patients were required to be diagnosed with Type 1 or 2 diabetes and have a glycosylated haemoglobin (HbA1c) of ≤12%, have visual impairment (BCVA of 78 to 24 letters) and with CRT ≥300 µm (or ≥ 320 µm on Spectralis) as determined by the reading centre at the screening visit. The trial excluded patients with evidence of macular oedema due to any cause other than diabetes mellitus in either eye, active proliferative diabetic retinopathy in the study eye, or uncontrolled diabetes or blood pressure. Patients were excluded if they had panretinal/macular laser photocoagulation or IVT anti-VEGF treatment in the study eye within 12 weeks of the screening visit.

6.9 The proposed PI for aflibercept 8 mg did not refer to CRT, level of visual impairment, method of diagnosis, use as monotherapy or in combination with laser photocoagulation. In clinical practice both treatment naïve, newly diagnosed, and prevalent patients are likely to receive treatment with aflibercept 8 mg. Approximately 45% of recruited patients included in PHOTON received prior DMO treatment. However, PHOTON did not report the duration of prior DMO treatment.

6.10 PHOTON included three treatment arms as described in Table 4. All three treatment arms undertook 4-weekly study visits.

6.11 Baseline characteristics for patients in PHOTON were generally well balanced across the three treatment arms. The mean age of study patients was 62 years, with approximately 63% male patients, a mean duration of diabetes of 15 years, a mean BCVA of 63 letters, and a mean CRT of 453 µm.

Table 4: Interventions compared in PHOTON

Treatment	Dosage regimen	Mean duration treatment, weeks (SD); 48-week analysis	Mean duration of treatment, weeks (SD); 60-week analysis
Aflibercept 2 mg 8-weekly	Aflibercept 2 mg IVT every 8 weeks, following 5 initial monthly doses	46.71 (6.893)	57.79 (9.727)
Aflibercept 8 mg 12-weekly	Aflibercept 8 mg IVT every 12 weeks, following 3 initial monthly doses. Shorter dose intervals were permitted from Week 24 up to Week 52, based on pre-specified criteria, and dose intervals of longer than 12 weeks (and up to 24 weeks) were permitted from Week 52 onwards.	45.67 (9.036)	56.48 (12.524)
Aflibercept 8 mg 16-weekly	Aflibercept 8 mg IVT every 16 weeks, following 3 initial monthly doses Shorter dose intervals were permitted from Week 28 up to Week 52 based on pre-specified criteria, and dose intervals of longer than 16 weeks (and up to 24 weeks) were permitted from Week 52 onwards.	47.10 (6.002)	58.45 (8.471)

Source: Table 2-12 p47 of the submission
IVT = intravitreal; SAF = safety analysis set; SD = standard deviation

6.12 In PHOTON, 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 (see paragraph 4.3). The mean number of injections of aflibercept 2 mg in PHOTON (estimated by the evaluation to be 14.97 for 2 years of treatment) was higher than the number of doses seen in Australian clinical practice, based on data from the Drug Utilisation Sub Committee (DUSC) Secretariat (dated September 2023), estimated by the submission (11.96 injections in 2 years, based on patients initiating treatment in 2020/2021).

6.13 Patients in the aflibercept 8 mg arms of PHOTON could extend dosing intervals in Year 2 only. This was inconsistent with the proposed PI where extension of treatment intervals can be considered after the initial loading doses (see paragraph 4.4). Additionally, in the aflibercept 8 mg treatment arms, treatment intervals in PHOTON could be extended up to 24 weeks, inconsistent with the draft PI submitted that proposed 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 mean number of aflibercept 8 mg injections in the first year of the PHOTON 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. The impact of these potential differences in dosing regimens on comparative effectiveness and safety is unclear. The Pre-Sub-Committee Response (PSCR) stated that differences between dosing regimens used in the trial and the longer dosing intervals in clinical practice are not expected to have any clinically relevant implications for comparative effectiveness because "longer dosing intervals will only be implemented in practice after empiric observation demonstrating individual patients continue to maintain efficacy as the treatment interval is extended". The PSCR claimed that the impact of the differences may be beneficial from a safety point of view because a lower frequency of ocular injections reduces the risk for injection related adverse events.

6.14 Additionally, the PSCR argued that it would be simpler for PBAC decision making to ignore the potential impact on health outcomes of these differences between trial based and real-world dosing frequencies because "they are applicable to both arms of the analysis and that instead the PBAC "should use the most conservative possible estimation of equi-effective dosing". The PSCR stated that this is the approach PBAC took in its consideration and recommendation of faricimab.

6.15 The primary outcome for PHOTON was the change in BCVA score from baseline, assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. 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 DMO (paragraph 6.12, faricimab DMO PSD, May 2022 PBAC meeting) and for the treatment of subfoveal choroidal neovascularisation (paragraph 6.11, brolucizumab PSD, November 2019 PBAC meeting).

6.16 The proportion of patients with a ≥2-step improvement from baseline at Week 48 in their diabetic retinopathy severity score (DRSS) was a key secondary endpoint for PHOTON. A non-inferiority margin of 15% was pre-specified for this outcome in PHOTON. This is less stringent than the 10% non-inferiority margin previously included for DRSS outcomes in the consideration of the faricimab submission in DMO (paragraph 6.13, faricimab DMO PSD, May 2022 PBAC meeting).

Comparative effectiveness

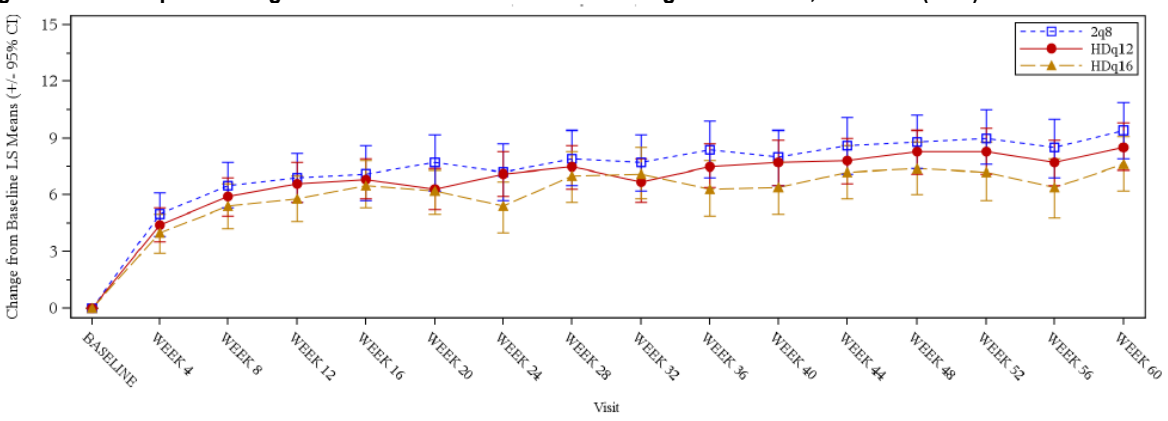
6.17 The results from PHOTON for the primary outcome, change in BCVA score from baseline averaged over Weeks 48, are presented in Table 5 and Figure 1. In all instances of comparison (at Week 48 and 60 and between 2q8 versus 8q12 and 8q16), the 95% CI included 0, indicating treatment differences were 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 5: Change from baseline in BCVA in PHOTON, (FAS;MMRM)

	8q12 (N=328)	8q16 (N=163)	2q8 (N=167)	8q12 vs 2q8	8q16 vs 2q8
				Treatment difference (95% CI)[a] Non-inferiority p-values	
Baseline BCVA (ETDRS letters score)	63.63	61.44	61.47		
Week 48					
Patients n (%)	277 (84.5%)	149 (91.4%)	150 (89.8%)	**–0.57 (–2.26, 1.13) <0.0001[b]**	**–1.44 (–3.27, 0.39) 0.0031[b]**
Mean change from baseline in BCVA (SD)	8.77 (8.95)	7.86 (8.38)	9.21 (8.99)		
LS mean change from baseline in BCVA (SE)	8.10 (0.61)	7.23 (0.71)	8.67 (0.73)		
Week 60					
Patients n (%)	252 (76.8%)	138 (84.7%)	133 (79.6%)	**–0.88 (–2.67, 0.91) 0.0003[b]**	**–1.76 (–3.71, 0.19) 0.0122[b]**
Mean change from baseline in BCVA (SD)	9.05 (9.27)	7.96 (9.14)	9.62 (9.58)		
LS mean change from baseline in BCVA (SE)	8.52 (0.63)	7.64 (0.75)	9.40 (0.77)		

Source: Table 2-16 p57, Table 2-17 p59 of the submission
Bolded values indicate statistical significance
BCVA = best corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; n = number of patients with event; FAS = full analysis set; MMRM = mixed model for repeated measurements; N = total patients in group; SE = standard error; SD = standard deviation; 2q8 = aflibercept 2 mg administered every 8 weeks; 8q12 = aflibercept 8 mg administered every 12 weeks; 8q16 = aflibercept 8 mg administered every 16 weeks;
a. Estimate for contrast was based on the MMRM model with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs Rest of World]; baseline CRT from reading centre [<400µm vs ≥400µm], prior treatment for DMO per EDC; [yes vs no]) as fixed factors, and terms for the interaction between baseline 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

Figure 1: Least square change from baseline in BCVA score through to Week 60, PHOTON (FAS)



Source: Figure 2-8 p60 of the submission
BCVA = best corrected visual acuity; CI = confidence intervals; HDq12 = aflibercept 8 mg administered every 12 weeks; HDq16 = aflibercept 8 mg administered every 16 weeks; FAS = full analysis set; 2q8 = aflibercept 2 mg administered every 8 weeks;

6.18 There was no statistically significant difference between aflibercept 8 mg (12-weekly or 16-weekly) and aflibercept 2 mg 8-weekly for the proportion of patients with a ≥2 step improvement on the DRSS, the proportion who gained ≥15 EDTRS letters, the proportion who gained ≥69 EDTRS letters, the proportion without fluid at foveal centre, or the change from baseline in the CRT at Week 48 and Week 60. However, there was a statistically significantly lower proportion of patients who experienced a

≥ 15 letters gain in BCVA at Week 60 in the 8q16 arm compared with 2q8 arm, and the mean change in CRT from baseline at Week 60 was statistically significantly lower in the 8q16 arm compared with 2q8 arm (Table 6 and Figure 2). The submission stated that these differences were not clinically relevant as non-inferiority in BCVA was demonstrated successfully. While this is likely to be reasonable, the differences may suggest a trend for increasing disparity between the 8q16 and 2q8 group outcomes over time. Whether those differences may eventually become clinically meaningful, and their applicability to Australian practice, is tempered by the more frequent T&E dosing schedule for aflibercept 2 mg (8 weekly in PHOTON compared with gradually increased treatment intervals in clinical practice) and less frequent dosing schedule for aflibercept 8 mg in Year 2 (24 weekly in PHOTON compared with up to 16 weekly in the proposed PI provided with the TGA Delegate's Overview).

Table 6: Results of secondary outcomes in PHOTON (FAS;MMRM, LOCF)

	8q12 (N=328)	8q16 (N=163)	2q8 (N=167)	8q12 vs 2q8	8q16 vs 2q8
				Treatment difference (95% CI) Superiority p-values[c]	
Proportion of patients gaining ≥ 15 letters in BCVA from baseline, n/N (%)[a]					
Week 48	61/326 (18.7%)	27/163 (16.6%)	38/165 (23.0%)	–4.64 (–12.30, 3.02) 0.2231	–7.14 (–15.45, 1.17) 0.0960
Week 60	70/326 (21.5%)	26/163 (16.0%)	43/165 (26.1%)	–5.01 (–13.04, 3.02) 0.2112	**–10.78 (–19.27, –2.29) 0.0143**
Mean change from baseline in CRT, µm[b]					
Mean baseline CRT (microns)	449.15	460.32	457.25		
Mean (SD) Week 48	–171.65 (141.52)	–148.30 (133.20)	–165.31 (140.22)	–11.92 (–30.30, 6.47) 0.2028	16.01 (–7.53, 39.54) 0.1817
LS (SE) Week 48	–176.77 (5.73)	–148.84 (9.45)	–164.85 (8.79)		
Mean (SD) Week 60	–176.24 (144.71)	–167.18 (127.18)	–191.31 (142.00)	12.21 (–3.74, 28.16) 0.1332	**27.90 (8.06, 47.74) 0.0060**
LS (SE) Week 60	–181.95 (6.09)	–166.26 (8.56)	–194.16 (7.15)		

Source: Table 2-19 p62, Table 2-22 p65 of the submission

Bolded values indicate statistical significance

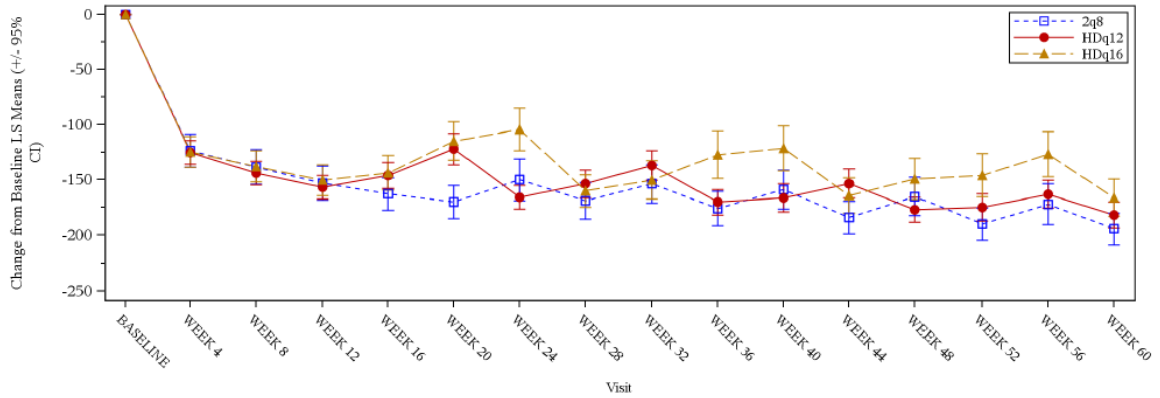
BCVA = best corrected visual acuity; CI = confidence interval; n = number of patients with event; CRT = central retinal thickness FAS = full analysis set; LOCF = last observation carried forward; MMRM = mixed model for repeated measurements; N = total patients in group; aflibercept; SE = standard error; SD = standard deviation; 2q8 = 2 mg administered every 8 weeks; 8q12 = aflibercept 8 mg administered every 12 weeks; 8q16 = aflibercept 8 mg administered every 16 weeks;

a. Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading centre) [<400 µm, ≥400 µm], prior DMO treatment [yes, no], geographical region [Rest of world, Japan]); Missing or ungradable baseline was not included in the denominator. The last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Participants were considered as non-responders if all post-baseline measurements were missing or non-gradable; FAS LOCF

b. Estimate for contrast was based on the MMRM model with baseline measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs Rest of World]; baseline CRT from reading centre [<400µm vs ≥400µm], prior treatment for DMO per EDC; [yes vs no]) as fixed factors, and terms for the interaction between baseline 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; FAS MMRM

c. p-value for superiority test;

Figure 2: Least square mean change from baseline in CRT (microns) through to Week 60, PHOTON (FAS)



Source: Figure 2-12 p67 of the submission
CI = confidence intervals; CRT = central retinal thickness FAS = full analysis set; HDq12 = aflibercept 8 mg administered every 12 weeks; HDq16 = aflibercept 8 mg administered every 16 weeks; 2q8 = aflibercept 2 mg administered every 8 weeks

6.19 Results of the improvement in quality of life as measured by the mean change from baseline in the National Eye Institute 25-item visual function questionnaire (NEI-VFQ-25) score from baseline are presented in **Table 7**. The improvement was comparable across treatment arms. While the mean number of injections received at Week 60 was lower in the 8q12 arm (6.6 injections) and 8q16 arm (5.9 injections) compared to the 2q8 arm (9.5 injections), PHOTON did not include a direct assessment of treatment burden; the NEI-VFQ-25 questionnaire (a health related quality of life questionnaire) does not contain items which are specific to treatment administration, or that would be anticipated to be affected by differences in the frequency of treatment administration without a corresponding difference in clinical efficacy.

Table 7: Change from baseline in NEI-VFQ-25 total score in the PHOTON trial (FAS; MMRM)

	8q12 (N=328)	8q16 (N=163)	2q8 (N=167)	8q12 vs 2q8	8q16 vs 2q8
				Treatment difference (95% CI) Superiority p-value[b]	
Change from baseline in NEI-VFQ-25 total score[a]					
Mean NEI-VFQ-25 score at baseline	76.79	77.86	76.65		
LS mean (SE)	4.06 (0.80)	2.94 (0.93)	2.82 (1.10)	1.25 (–1.09, 3.58) 0.2941	0.13 (–2.37, 2.62) 0.9208
Mean (SD)	5.64 (12.56)	4.16 (10.94)	4.41 (13.84)		

Source: Table 2-24 p68 of the submission
CI = confidence intervals; CRT = central retinal thickness; DMO = diabetic macular oedema; EDC = electronic data capture; FAS = full analysis set; LS = least square; MMRM = mixed model for repeated measurements; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire 25; SD = standard deviation; SE = standard error; 2q8 = aflibercept 2 mg administered every 8 weeks; 8q12 = aflibercept 8 mg administered every 12 weeks; 8q16 = aflibercept 8 mg administered every 16 weeks;
a. Estimate for contrast was based on the MMRM model with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs Rest of World]; baseline CRT from reading centre [<400µm vs ≥400µm], prior treatment for DMO per EDC; [yes vs no]) as fixed factors, and terms for the interaction between baseline 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. Nominal p-value for superiority test

Comparative harms

6.20 A summary of safety outcomes for PHOTON to Week 60 is presented in Table 8.

6.21 The incidence of adverse events (AEs) and treatment-emergent adverse events (TEAEs) was comparable between treatment arms in PHOTON. No significant treatment differences for study drug related TEAEs, IVT injection procedure related TEAEs, procedure related TEAEs, fellow eye treatment related TEAEs or serious TEAEs were observed among treatment arms in PHOTON (Table 8). However, PHOTON was not powered for direct comparisons of AEs between the study groups.

6.22 The most common ocular TEAEs in the study eye were eye disorders (32.9%, 33.1% and 25.7% in the 8q12, 8q16 and 2q8 arms), and mostly included cataract, conjunctival haemorrhage, diabetic retinal oedema, eye pain, punctate keratitis, retinal haemorrhage, vitreous detachment, and vitreous floaters, all of which occurred at similar frequencies (≤5%) in all treatment arms. Reported events were consistent with the known safety profile of IVT aflibercept.

Table 8: Summary of key adverse events in PHOTON, (SAF)

Outcome	8q12 (N=328) n (%)	8q16 (N=163) n (%)	2q8 (N=167) n (%)	8q12 vs 2q8		8q16 vs 2q8	
				OR (95% CI)	RD (95% CI)	OR (95% CI)	RD (95% CI)
				OR<1 favours 8q12/8q16; RD<0 favours 8q12/8q16			
Any AE	247 (75.30%)	128 (78.53%)	124 (74.25%)	1.06 (0.69,1.62)	0.01 (–0.07,0.09)	1.27 (0.76, 2.11)	0.04 (–0.05, 0.13)
Any TEAE	245 (74.70%)	126 (77.30%)	123 (73.65%)	1.06 (0.69,1.61)	0.01 (–0.07, 0.09)	1.22 (0.74, 2.01)	0.04 (–0.06, 0.13)
Ocular TEAE	147 (44.82%)	73 (44.79%)	73 (43.71%)	1.05 (0.72, 1.52)	0.01 (–0.08, 0.10)	1.04 (0.68, 1.61)	0.01 (–0.10, 0.12)
Non-ocular TEAE	195 (59.45%)	104 (63.80%)	96 (57.49%)	1.08 (0.74, 1.58)	0.02 (–0.07, 0.11)	1.30 (0.84, 2.03)	0.06 (–0.04, 0.17)
Study drug-related TEAE	6 (1.83%)	1 (0.61%)	3 (1.80%)	1.02 (0.25, 4.12)	0.00 (–0.02, 0.03)	0.34 (0.03, 3.28)	–0.01 (–0.04, 0.01)
Injection procedure related TEAE	45 (13.72%)	13 (7.98%)	19 (11.38%)	1.24 (0.70, 2.19)	0.02 (–0.04, 0.08)	0.68 (0.32, 1.42)	–0.03 (–0.10, 0.03)
Study-conduct related TEAE	6 (1.83%)	0 (0.00%)	3 (1.80%)	1.02 (0.25, 4.12)	0.00 (–0.02, 0.03)	0.14 (0.01, 2.80)	–0.02 (–0.04, 0.01)
TEAE leading to discontinuation of study drug	9 (2.74%)	2 (1.23%)	3 (1.80%)	1.54 (0.41, 5.77)	0.01 (–0.02, 0.04)	0.68 (0.11, 4.12)	–0.01 (–0.03, 0.02)
Any serious TEAE	65 (19.82%)	29 (17.79%)	36 (21.56%)	0.90 (0.57, 1.42)	–0.02 (–0.09, 0.06)	0.79 (0.46, 1.36)	–0.04 (–0.12, 0.05)
Ocular serious TEAE	6 (1.83%)	2 (1.23%)	5 (2.99%)	0.60 (0.18, 2.01)	–0.01 (–0.04, 0.02)	0.40 (0.08, 2.10)	–0.02 (–0.05, 0.01)
Non-ocular serious TEAE	61 (18.60%)	27 (16.56%)	32 (19.16%)	0.96 (0.60, 1.55)	–0.01 (–0.08, 0.07)	0.84 (0.48, 1.47)	–0.03 (–0.11, 0.06)
Any death	9 (2.74%)	4 (2.45%)	5 (2.99%)	0.91 (0.30, 2.77)	–0.00 (–0.03, 0.03)	0.82 (0.21, 3.09)	–0.01 (–0.04, 0.03)
Adjudicated TE APTC events	13 (3.96%)	9 (5.52%)	6 (3.59%)	1.11 (0.41, 2.97)	0.00 (–0.03, 0.04)	1.57 (0.55, 4.51)	0.02 (–0.03, 0.06)
TEAE of intraocular inflammation	4 (1.22%)	1 (0.61%)	1 (0.60%)	2.05 (0.23, 18.48)	0.01 (–0.01, 0.02)	1.02 (0.06, 16.52)	0.00 (–0.02, 0.02)
TEAE of hypertension	42 (12.80%)	28 (17.18%)	23 (13.77%)	0.92 (0.53, 1.59)	–0.01 (–0.07, 0.05)	1.30 (0.71, 2.36)	0.03 (–0.04, 0.11)
TEAE of nasal mucosal finding	0 (0.00%)	0 (0.00%)	0 (0.00%)	Not estimable	0.00 (–0.01, 0.01)	Not estimable	0.00 (–0.01, 0.01)

Source: Table 2-25 p70-74 of the submission

AE = adverse events; APTC = Antiplatelet Trialists' Collaboration; CI = confidence intervals; n = number of patients with event; N = total number of patients in treatment arm; OR = odds ratio; RD = risk difference; SAE = serious adverse events; SAF = safety analysis set; TEAE = treatment-emergent adverse events; 2q8 = aflibercept 2 mg administered every 8 weeks; 8q12 = aflibercept 8 mg administered every 12 weeks; 8q16 = aflibercept 8 mg administered every 16 weeks;

OR and RD (and associated 95%CI) calculated by the submission, post-hoc using Review Manager version 5.4

TEAE was an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who were still participating in the study (i.e., had not been withdrawn) as of the Week 60 visit all AEs up through the date of the last visit were to be considered treatment-emergent. A pre-treatment AE was an AE starting from signing the informed consent form to before the first dose of study drug. A post-treatment AE was an AE starting after the end of the on-treatment (TEAE) period.

6.23 Death occurred in 2.74% of patients in the 8q12 group, 2.45% of patients in 8q16 group, and 2.99% of patients in the 2q8 group. None of the reported deaths were deemed to be related to study treatment.

Benefits/harms

6.24 Given the claim of non-inferiority for aflibercept 2 mg versus aflibercept 8 mg, a comparison of benefits and harms was not presented.

Clinical claim

6.25 The submission described aflibercept 8 mg (administered 12-weekly or 16-weekly) as non-inferior to aflibercept 2 mg (administered 8-weekly) in terms of effectiveness and safety in patients with visual impairment due to DMO. The therapeutic conclusion with respect to the primary outcome and the majority of the secondary outcomes was adequately supported by the evidence presented in the submission. The submission considered that the differences in two secondary outcomes (proportion of patients with $\geq$ 15 letters in BCVA and CRT thickness) between aflibercept 8 mg (q16) and aflibercept 2 mg at 60 weeks were not clinically meaningful as the pre-defined criteria for non-inferiority based on BCVA were met.

6.26 The submission also claimed that while maintaining similar efficacy outcomes, extended treatment intervals (up to 24 weeks) for aflibercept 8 mg provide a meaningful reduction in the frequency of treatment administration and therefore potentially reduced treatment burden in patients with DMO.

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

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

Economic analysis

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

6.30 The submission presented the CMA over a 2-year time horizon to account for induction dosing for newly diagnosed/treatment naive patients 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 DMO PSD, May 2022 PBAC meeting).

6.31 The key components and assumptions of the CMA are presented in Table 9.

Table 9: Summary of analysis structure, key inputs, and rationale (as proposed in the submission)

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 PHOTON trial. Drug utilisation was informed by PHOTON for aflibercept 8 mg and in-market data (from the DUSC Secretariat) for aflibercept 2 mg.
Equi-effective doses	Year 1: 6.20 doses of aflibercept 8 mg to 6.68 doses of aflibercept 2 mg Year 2: 3.67 doses of aflibercept 8 mg to 5.28 doses of aflibercept 2 mg
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 = $329.40*

Source: Table 3-2 p101 of the submission.
AEMP = ex-manufacturer price; DUSC = Drug Utilisation Sub Committee; MBS = Medicare Benefits Schedule
*Fee for MBS item 42738 at the time of commentary was $331.05.

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

6.33 The equi-effective number of doses of aflibercept 8 mg in Year 1 was estimated as 6.20 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 PHOTON are likely to reflect more doses in Year 1 than would be observed in clinical practice given that the dosing regimen in PHOTON did not allow extensions in the treatment interval in Year 1.

6.34 The equi-effective number of doses of aflibercept 8 mg in Year 2 was estimated as 3.67 injections and was estimated from the distribution of patients on each dosing interval at 96 weeks. Patients on a 24-week dosing interval were pooled with the 20-week dosing interval. The evaluation stated that pooling of patients was appropriate given the draft PI provided with the submission proposed that the treatment interval for aflibercept 8 mg could be extended up to a maximum of 20 weeks.

6.35 Based on in-market PBS data provided by the DUSC Secretariat, the average number of doses of aflibercept 2 mg was 6.68 injections in Year 1 and 5.28 injections in Year 2 (11.96 doses for Years 1 and 2). Given the dosing regimen of aflibercept 2 mg in the PHOTON trial was not representative of T&E regimens in Australian clinical practice, the evaluation and the ESC considered use of in-market data 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; 6.38 doses, Year 2; 5.27 doses) (paragraph 7.2, faricimab DMO PSD, May 2022 PBAC meeting).

6.36 The approach adopted by the submission 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. A secondary analysis presented by the sponsor estimated the mean doses

in Year 1 and Year 2 by considering only those patients who stayed on treatment in Years 2 and 3. This resulted in a higher equi-effective dose for aflibercept 2 mg. The ESC considered the submission's approach of including patients who discontinued to be conservative against aflibercept 8 mg.

6.37 Based on the data and relativities presented above, the submission concluded that 6.20 doses of aflibercept 8 mg and 6.68 doses of aflibercept 2 mg are equi-effective for Year 1 and 3.67 doses of aflibercept 8 mg and 5.28 doses of aflibercept 2 mg are equi-effective for Year 2.

6.38 The submission included cost offsets associated with differences in the frequency of administering aflibercept 8 mg and aflibercept 2 mg in the CMA. The submission did not include the cost of monitoring for either treatment which may include assessment of visual acuity, measurement of intraocular pressure, check for perfusion of optic nerve or tonometry. The ESC considered the exclusion of monitoring costs may be conservative against aflibercept 8 mg.

6.39 The results of the CMA are presented in Table 10 and are based on the proposed effective prices.

Table 10: 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)	$[redacted][b]	
Aflibercept 8 mg frequency of administration over 2 years	9.87	
Total cost of aflibercept 8 mg	$[redacted]	
Aflibercept 2 mg cost per administration (AEMP)		$[redacted]
Aflibercept 2 mg frequency of administration over 2 years		11.96
Total cost of aflibercept 2 mg		$[redacted]
Administration cost		
Unit cost per administration (MBS item: 42738)	$331.05[a]	$331.05[a]
Total administration cost	$3,266.31[b]	$3,959.36[b]
Total cost of drug over 2 years	$[redacted][b]	$[redacted][b]

Source: Table 3-7, p108 of the submission.

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule; mg = milligram

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.

[a] Corrected during the evaluation based on the updated unit cost for MBS item: 42738 as at November 2023

[b] Revised estimates corrected during the evaluation using updated unit cost for MBS item: 42738

6.40 The evaluation estimated that based on data from PHOTON, the mean number of doses of aflibercept 2 mg for the 2-year time horizon was 14.97. This was estimated by applying the same approach utilised by the submission in calculating the mean dose of aflibercept 8 mg in Year 1; the mean active injections at 96 weeks (12.89) were adjusted for mean treatment duration at 96 weeks (89.51 weeks) and apportioned to 104 weeks. Applying the trial based mean number of doses for aflibercept 2 mg, increased the cost-minimised price (AEMP) for aflibercept 8 mg. Using data from PHOTON would overestimate the number of aflibercept 2 mg doses as the dosage interval was fixed and the study protocol did not allow for a T&E approach.

6.41 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 PHOTON. The 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 PHOTON clinical trial and implemented in the cost-minimisation. The ESC noted the maximum time between doses of aflibercept 8 mg in PHOTON (24 weeks) is longer than that recommended in the proposed Product Information (20 weeks) 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 PHOTON 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 11).

6.42 The PSCR added that the cost-minimisation implicitly assumed the lower dosing frequency in the comparator arm of the analysis (i.e. aflibercept 2 mg) has the same health outcomes of the more frequent trial based regimens, and that taken together, this means the cost-minimisation uses a dosing frequency for aflibercept 8 mg which 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.

6.43 The PSCR added that "deriving mean doses based on the trial data is likely to be biased against aflibercept 8 mg (overstating the number of injections in practice)." The PSCR and the pre-PBAC response stated that the approach used by the submission to calculate the equi-effective dose of aflibercept 8 mg in Years 1 and 2 was consistent with the approach accepted by the PBAC for the listing of faricimab on the PBS and that this was appropriate given the clinical evidence available for aflibercept 8 mg".

6.44 The PSCR additionally stated that the submission presented a secondary analysis to demonstrate the mean dose of aflibercept 2 mg when the PBAC guidelines for calculating equi-effective doses of medicines for ongoing treatment, the use of 'steady state' dose comparison (i.e., the average dose after dose titrations is complete and after excluding participants who discontinue the medicine) were applied, and that this demonstrated that the base case analysis was conservative.

6.45 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 doses and so would be expected to have the same number of

aflibercept 2 mg injections in year 1 as in year 2 (i.e., 5.28 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….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".

6.46 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" [rather than a 20-week interval], the pre-PBAC response presented a revised CMA based on a maximum treatment interval of 16 weeks (see Table 11 below).

Table 111: Summary: **Results of the cost-minimisation approach – REVISED**

Component	Aflibercept 8 mg	Aflibercept 2 mg
Treatment cost		
Aflibercept 8 mg cost per administration (AEMP)	$[redacted] (previously $[redacted])	
Aflibercept 8 mg frequency of administration over 2 years	10.15[1] (previously 9.87)	
Total cost of aflibercept 8 mg	$[redacted]	
Aflibercept 2 mg cost per administration (AEMP)		$[redacted]
Aflibercept 2 mg frequency of administration over 2 years		11.96
Total cost of aflibercept 2 mg		$[redacted]
Administration cost		
Unit cost per administration (MBS item: 42738)	$331.05	$331.05
Total administration cost	$3,359.46	$3,959.36
Total cost of drug over 2 years	$[redacted]	$[redacted]

Source: pre-PBAC response

1. 6.20 injections in the 1st year PLUS 3.95 injections in the 2nd year.

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

6.48 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

6.49 The drug cost per patient per year is presented in Table 12 using the effective prices of aflibercept 8 mg and aflibercept 2 mg. The cost per patient per year for aflibercept 2 mg was higher based on use of the mean number of doses in the PHOTON trial.

6.50 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 12: 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	4.875[a]	5.075[b]	5.075[b]	7.485[c]	5.98[d]	5.98[d]
DPMQ per script		$			$	
Cost/patient/year	$	$	$	$	$	$

Source: constructed during the evaluation based on Section 3 and Section 4 of the Submission.
CMA= cost-minimisation approach; mg = milligrams.
[a] Averaged over 2-years treatment including 24-week interval doses (6.20 doses in Year 1 and 4.94 doses in Year 2).
[b] Averaged over 2-years treatment, assuming a maximum treatment interval of 16 weeks as proposed in the TGA Delegate's Overview (6.20 doses in Year 1 and 3.95 doses in Year 2).
[c] Average of the total number of doses (14.97 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 (6.68 doses in Year 1 and 5.28 doses in Year 2).

Estimated PBS usage & financial implications

6.51 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 DMO was estimated from the historical use of aflibercept 2 mg and ranibizumab for DMO. The sources of data utilised are shown in Table 13.

Table 13: Key inputs for financial estimates

Data	Value applied and source	Comment
Treatment utilisation		
Anti-VEGF market without listing of aflibercept 8 mg		
Estimated anti-VEGF market for 2022 (scripts)	103,426 Medicare statistics. Estimated as the number of scripts for aflibercept 2 mg and ranibizumab for DMO	
Annual market growth (in scripts)	9,500 in Year 1 to 8,500 in Year 6 The submission assumed a diminishing market growth by arguing it will capture the faricimab market share where fewer scripts will be used compared to aflibercept 2 mg and ranibizumab.	Annual increase in number of scripts at a diminishing rate may be reasonable as faricimab requires fewer injections and results in a smaller number of scripts. The estimated decline (500 scripts every two years) was uncertain.
Projected market size of the current anti-VEGF treatments	From 122,926 scripts in Year 1 to 167,426 scripts in Year 6 Calculated 2022 scripts for anti-VEGF treatments and the assumed annual growth of anti-VEGF market	Refer to comment above.

Data	Value applied and source	Comment
Share of current market (status quo scenario without listing of aflibercept 8 mg)	Aflibercept 2 mg: [redacted]% in Year 1 declining to [redacted]% in Year 6 Ranibizumab: [redacted]% in Year 1 declining to [redacted]% in Year 6 Faricimab: [redacted]% in Year 1 increasing to [redacted]% in Year 6 Share of aflibercept 2 mg and ranibizumab were based on historical trend of respective drugs in the absence of faricimab. Sponsor assumed market share of faricimab to be [redacted]% in 2023 and projected to [redacted]% in Year 6 with constant growth.	The assumed market share of faricimab for year 2023 (15%) is consistent with the market share of faricimab observed for year 2023 (12.5%, until September 2023) from Medicare statistics sourced during the evaluation. No justification was provided for the 35% assumed for Year 6.
Distribution of treatment type (initiation and continuation) in the current market	Aflibercept 2 mg and ranibizumab: 30%/70% split for initiation/continuation for the 6 years period. Faricimab: 43%/57% split for Year 1 and 33%/67% split for subsequent years per initiation/continuation Observed historical utilisation trend of ranibizumab and aflibercept 2 mg sourced from May 2018 DUSC report and faricimab DMO PSD, May 2022 PBAC meeting. Distribution of initiation and continuation scripts for faricimab was estimated by adjusting historical aflibercept/ranibizumab utilisation 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		
Uptake rate (rate of substitution)	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.	The ESC considered that the uptake of aflibercept 8 mg and substitution of other VEGF-I including aflibercept 2 mg and faricimab was uncertain. The ESC considered that substitution rates may be higher and that this would result in a higher cost to the PBS/RPBS due to the need for additional loading doses.
Distribution of treatment type (initiation/ continuation)	Aflibercept 8 mg: starting with initiation/continuation split of 77%/23% in Year 1 and declining to 38%/62% from Year 4 Observed historical utilisation trend of ranibizumab and aflibercept 2 mg sourced from May 2018 DUSC report and faricimab DMO PSD, May 2022 PBAC meeting	
Script equivalence	Aflibercept 2 mg Initial scripts: 1:1; Continuing scripts: 0.75; Continuing scripts to initial scripts: 2.27 Faricimab Initial scripts: 1:1; Continuing scripts: 0.84; Continuing scripts to initial scripts: 2.56	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

Data	Value applied and source	Comment
		though the maximum dosing interval is the same (16 weeks).
Number of scripts estimated for aflibercept 8 mg	From 10,430 in Year 1 to 61,682 in Year 6 Calculated as the sum of the projected scripts uptake from aflibercept 2 mg and faricimab per distribution of treatment type.	
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, p110; Table 4-3, p112; Table 4-4, p113; Table 4-9, p116; Table 4-11, p117; Table 4-13, p119; Table 4-14, p120, Table 4-16, p121 and Workbook 'Aflibercept8mg_Section4_DMO_Nov2023' of the submission.
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

6.52 The submission relied on a number of assumptions to derive the uptake rate for aflibercept 8 mg from aflibercept 2 mg and faricimab. Overall, the submission predicted that the introduction of aflibercept 8 mg into the current DMO market will result in 43% of all DMO patients receiving aflibercept 8 mg for PBS-subsidised anti-VEGF maintenance treatment in Year 6 of its listing.

6.53 The estimated utilisation and financial impact of listing aflibercept 8 mg, with script equivalence being based on a maximum treatment interval for aflibercept 8 mg of 16 weeks and using the effective price for aflibercept 2 mg and the assumed effective price for faricimab is presented in Table 14.

Table 14: Estimated use and financial implications (effective price of aflibercept 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]	[2]	[3]	[4]	[6]
Estimated financial implications of aflibercept 8 mg						
Cost to PBS/RPBS less copayments	[6]	[6]	[7]	[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	[6]	[6]	[6]	[6]	[6]	[6]
Net cost to MBS	[9]	[9]	[9]	[9]	[9]	[9]
Net cost to Government	[6]	[6]	[6]	[6]	[6]	[6]

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

mg = milligram; PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefit Scheme.

The redacted values correspond to the following ranges:

[1] *10,000 to < 20,000*

[2] *20,000 to < 30,000*

[3] *30,000 to < 40,000*

[4] *50,000 to < 60,000*

[5] *60,000 to < 70,000*

[6] *$0 to < $10 million*

[7] *$10 million to < $20 million*

[8] *$20 million to < $30 million*

[9] *net cost saving*

6.54 The total cost to the PBS/RPBS of listing aflibercept 8 mg was estimated to be $0 to < $10 million in Year 1 and $100 million to < $200 million over the first 6 years of listing. The net cost to the PBS/RPBS, after accounting for substitution of aflibercept 2 mg (using the effective price) and faricimab (using the assumed effective price), was $0 to < $10 million in Year 1 and $10 million to < $20 million over the first 6 years of listing. The net cost to the PBS/ RPBS was higher in the first 3 years of listing due to the higher proportion of initial scripts which accounted for the loading doses.

6.55 The total cost to the PBS/RPBS was partially offset by a reduction of MBS costs associated with 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 $0 to < $10 million over the first 6 years of listing.

6.56 The PSCR stated that ultimately there will be cost savings to the PBS/RPBS in the longer term, despite the inclusion of administration cost offsets because the pricing of aflibercept 8 mg incorporates the higher dosing frequency in the first year of a two-year time horizon whereas patients will continue aflibercept 8 mg for much longer. As the share of maintenance dosing increases over time, the PSCR claimed that the savings to the PBS/RPBS from the lower annual cost of maintenance dosing with aflibercept 8 mg compared to that of aflibercept 2 mg will more than offset the loading dose effect seen in the six-year timeframe of the budget impact analysis.

6.57 The ESC disagreed with the PSCR, considering that there would still be a net cost to the Australian healthcare system. The ESC noted this net cost was based on the need for patients switching from aflibercept 2 mg to aflibercept 8 mg to receive re-loading doses of aflibercept.

6.58 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.

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 due to diabetic macular oedema (DMO). 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 PHOTON trial, a non-inferiority study that compared aflibercept 8 mg (12-weekly or 16-weekly) and aflibercept 2 mg (8-weekly). 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 the loading doses (3 monthly injections for aflibercept 8 mg and 5 monthly injections for aflibercept 2 mg). Additionally, the PBAC noted the treatment interval for aflibercept 8 mg could be extended up to 24 weeks (based on response) which was not consistent with the draft Product Information, where the maximum recommended treatment interval will be 16 weeks (as agreed to by the sponsor).

7.6 The PBAC considered the claim of non-inferior comparative efficacy to be adequately supported, noting 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 arms in PHOTON. The PBAC considered that the claim of non-inferior safety 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 PHOTON trial were not consistent with clinical practice (as discussed in paragraphs 6.12 and 6.13). 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 10.15 injections of aflibercept 8 mg (6.2 injections in Year 1, 3.95 injections in Year 2) were equi-effective to 11.96 injections of aflibercept 2 mg (6.68 injections in Year 1, 5.28 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, given the need for re-loading doses for patients switching to aflibercept 8 mg. 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 included in the pre-PBAC response (10.15 vs 11.96 doses over 2 years, respectively) were more favourable for aflibercept 8 mg than the previously determined equi-effective doses for faricimab and aflibercept 2 mg (12.91 vs 11.65 doses over two years, 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 12.91 doses of aflibercept 8mg/ faricimab and 11.65 doses of aflibercept 2 mg/ ranibizumab, as follows:

- Year 1: 8.23 injections of aflibercept 8 mg/ faricimab to 6.38 injections of aflibercept 2 mg/ ranibizumab
- Year 2: 4.68 injections of aflibercept 8 mg/ faricimab to 5.27 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 14) resulted in a net cost to the PBS/RPBS over the first 6 years of listing. The PBAC noted this was due in part 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 was appropriate, that it should be in operation for a maximum of 12 months from listing and that the following administrative advice 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	5	Eylea
Continuing treatment					
aflibercept 8 mg/0.07 mL injection, 0.07 mL vial	NEW	1	1	5	Eylea
Restriction Summary edit 13342 / Treatment of Concept: edit 13388					
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 may be requested through the same authority application.					
Indication: Diabetic macular oedema (DMO)					
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:					
Patient must have visual impairment due to diabetic macular oedema					
AND					
Clinical criteria:					
Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment					
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 as monotherapy; or					
The treatment must be in combination with laser photocoagulation					
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 13414 / Treatment of Concept: edit 13402
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED) [new code]
Indication: Diabetic macular oedema (DMO)
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:
Patient must have previously received PBS-subsided treatment with this drug for this condition for the same eye
AND
Clinical criteria:
The treatment must be as monotherapy; or
The treatment must be in combination with laser photocoagulation
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
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 13342 / Treatment of Concept: edit 13388
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
Indication: Diabetic macular oedema (DMO)
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:
Patient must have visual impairment due to diabetic macular oedema
AND
Clinical criteria:
Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment
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 as monotherapy; or
The treatment must be in combination with laser photocoagulation
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
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: 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.