

5.02 FARICIMAB,

Solution for intravitreal injection 28.8 mg in 0.24 mL vial,

Solution for intravitreal injection 24.0 mg in 0.2 mL syringe,

Vabysmo[®],

Roche Products Pty Limited.

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required listing for faricimab for the treatment of neovascular age-related macular degeneration (nAMD).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus aflibercept, as a proxy for standard of care (vascular endothelial growth factor (VEGF) inhibitors).
- 1.3 A concurrent submission for faricimab for the treatment of diabetic macular oedema (DMO) was considered at the May 2022 intracycle PBAC meeting.

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

Component	Description
Population	Patients with nAMD
Intervention	Faricimab intravitreal injection
Comparator	Aflibercept intravitreal injection, as a proxy for standard of care VEGF inhibitors
Outcomes	Best corrected visual acuity (BCVA); proportion of patients gaining/avoiding a loss of ≥ 15 letters in BCVA; change in central subfield thickness; quality of life; ocular and non-ocular adverse events
Clinical claim	In patients with nAMD, faricimab is non-inferior to aflibercept in terms of efficacy, with fewer injections and a comparable safety profile.

Source: Table 1.1, p.2 of the submission

Abbreviations: nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor

2 Background

Registration status

- 2.1 The submission was submitted under the TGA/PBAC parallel process, and is being evaluated under the Access Consortium New Active Substance Work-Sharing Initiative. The TGA delegate's overview was available at the time of PBAC consideration. While a decision was yet to be made, the TGA delegate noted that they were inclined to approve the registration of the product.
- 2.2 The proposed TGA indication is for the treatment of:
 - neovascular (wet) age-related macular degeneration (nAMD); and
 - diabetic macular oedema.

- 2.3 Faricimab was approved for use by the US Food and Drug Administration on 28 January 2022 to treat nAMD and DMO. Faricimab is currently under evaluation by the European Medicines Agency.

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

3 Requested listing

- 3.1 The submission requested the following restriction for nAMD. Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FARICIMAB					
<i>faricimab</i> 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	35	Vabysmo
<i>faricimab</i> 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	35	Vabysmo
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone <i>Written</i>					
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 on the same authority prescription form.					
Administrative Advice: Pharmaceutical benefits that have the form <i>faricimab</i> 0.24 mL injection vial and pharmaceutical benefits that have the form <i>faricimab</i> 0.2 mL injection syringe are equivalent for the purposes of substitution.					
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					
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 Instructions:					
Authority approval for initial treatment of each eye must be sought.					

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	<p>Prescribing Instructions: The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<i>FARICIMAB</i>					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	51	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	51	Vabysmo

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Telephone (<i>STREAMLINED</i>)
	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
	AND
	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 been granted an authority prescription for the same eye
	AND
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
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FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	0	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	0	Vabysmo
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Written				
	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				
	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:				
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]				
	AND				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>				
	Administrative Advice: <i>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.</i>				
	Prescribing Instructions: <i>The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report.</i>				

- 3.2 The proposed restriction includes two faricimab formulations (28.8 mg/0.24 mL vial; 24.0 mg/0.2 mL pre-filled syringe). However, the submission noted that at the time of lodgement, a regulatory application had only been lodged for the faricimab vial formulation. The Pre-PBAC Response clarified that a syringe form is also being requested for PBS listing.
- 3.3 The published dispensed price for maximum quantity (DPMQ) for faricimab is the same as for VEGF inhibitors listed on the PBS, aflibercept and ranibizumab. The same price is proposed in the faricimab submission for DMO. The submission requested a special pricing arrangement, with the effective price to be calculated based on the effective price of the main comparator, aflibercept, on a 1:1 injection basis.

- 3.4 The submission requested a maximum quantity of one injection, with five repeats. The PBS listings for aflibercept and ranibizumab for nAMD have two repeats, consistent with the number of prescriptions required to provide three four-weekly loading doses, as specified in their product information documents. The faricimab draft product information specifies four four-weekly loading doses, consistent with three repeats, however the submission stated that five repeats were sought based on clinician feedback (not provided), to ensure consistency with the DMO restriction which has five repeats (of which, in DMO, three loading doses are specified for ranibizumab and five loading doses for aflibercept) and reduce prescription administrative burden. The Secretariat suggested the maximum repeats for faricimab be revised to 3 (initial), 1 (continuing) and 0 (grandfather) based on the draft faricimab PI dosing instructions. The PBAC considered that 2 repeats would be appropriate for faricimab for all treatment phases to maintain consistency with aflibercept and ranibizumab listings for the same indication, noting some patients receive these medicines under treat-and-extend regimens.
- 3.5 The submission requested a General Schedule Authority required (telephone) listing for initial and continuing patients and Authority required (in writing) for grandfathered patients, for the treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD). This is consistent with the proposed TGA indication, but is broader than the key TENAYA and LUCERNE trials (the trials were limited to treatment naïve patients, aged ≥ 50 years, with BCVA 78-24 letters). The PBAC considered that the faricimab listing should be consistent with the restrictions for aflibercept and ranibizumab for the above criteria.
- 3.6 The proposed restriction is consistent with the PBS restrictions for aflibercept and ranibizumab for nAMD. However, the faricimab submission requested a telephone authority for initial treatment (aflibercept and ranibizumab have written authorities for initial treatment), although the administrative advice states that the first authority application must be made in writing. The PBAC considered that a Written authority would be more appropriate for patients initiating faricimab to be consistent with its comparators.
- 3.7 The requested authority for continuing patients was Authority Required – Telephone, consistent with the current restrictions for aflibercept and ranibizumab. The PBAC recalled that, at its November 2021 meeting, it had recommended that the restriction level for patients continuing aflibercept, dexamethasone and ranibizumab should be lowered to Authority Required (STREAMLINED) to reduce administrative burden for specialist clinicians and improve timely access to treatment for patients (PBAC Meeting Outcomes, November 2021). The PBAC considered that the continuing restriction for faricimab should also be Authority Required (STREAMLINED) to be consistent with the November 2021 recommendation.
- 3.8 The submission requested grandfathered treatment of patients with nAMD. The submission stated that an estimate of eligible grandfathered patients could be

provided to the Department of Health if faricimab receives a positive PBAC recommendation. The PBAC noted that given the small number of Australian patients who participated in the clinical trials (38 patients in the LUCERNE trial), the proposed grandfathering provisions are unlikely to substantially affect the financial estimates. The PBAC considered that a grandfather restriction would be appropriate and recommended the grandfather listing be in operation for a maximum of 12 months from listing.

- 3.9 The PBAC noted the proposed initial restriction Administrative advice regarding a-flagging between the two forms and considered that faricimab 0.24 mL injection vial and faricimab 0.2 mL injection syringe should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution).
- 3.10 The PBAC recalled that brolocizumab was previously accepted as a subsequent therapy after aflibercept or ranibizumab and considered that this should also apply to faricimab (paragraph 7.4, brolocizumab Public Summary Document [PSD], March 2021 PBAC meeting). The PBAC considered that upon listing of faricimab for nAMD, the restriction flow-on change should apply to the following brolocizumab initial and grandfather restriction: "Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of treatment with: 1. Aflibercept and/or 2. Ranibizumab and/or 3. Faricimab".

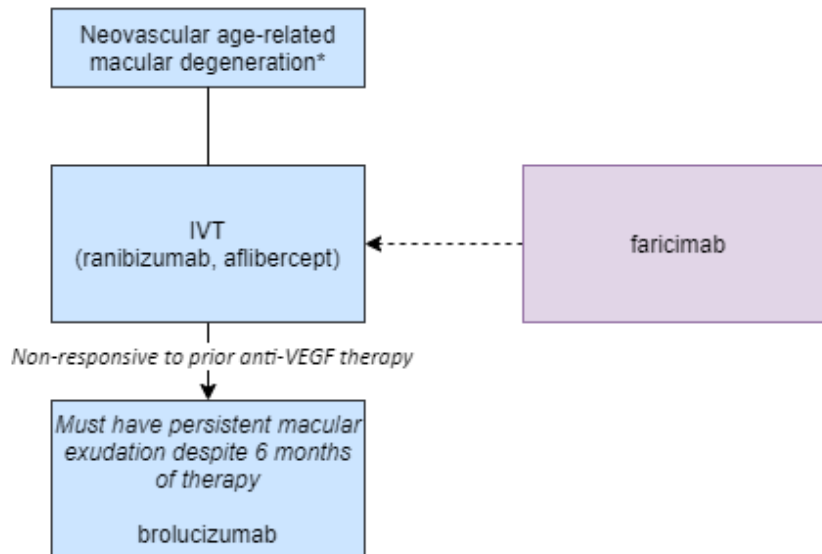
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Age-related macular degeneration is a chronic eye disease characterised by progressive degenerative abnormalities in the central retina (macula) and is the leading cause of severe vision loss and legal blindness in people over the age of 65 years. Neovascular (wet) AMD (nAMD) occurs in around 10-15% of overall AMD cases and is characterised by choroidal neovascularisation, a process in which new blood vessels grow beneath the retina and macula. These abnormal blood vessels may leak fluid and/or blood and penetrate the photoreceptor layer, resulting in focal retinal detachment and rapid central vision loss (Bhutto 2012; van Lookeren Campagne 2014), and potential blindness (Wong 2014).
- 4.2 The submission claimed that current standard of care with VEGF inhibitors is associated with frequent intravitreal injections and office visits (and associated out-of-pocket costs) which contribute to many patients not achieving or maintaining vision outcomes comparable with those observed in controlled clinical trials. The submission claimed that there is a significant unmet need for novel interventions that reduce treatment burden, subsequently reducing patient clinic visits for treatment administration.

- 4.3 Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2). Inhibition of VEGF-A suppresses endothelial cell proliferation, neovascularisation and vascular permeability, and inhibition of Ang-2 is thought to promote vascular stability and desensitise blood vessels to the effects of VEGF-A.
- 4.4 Faricimab dosing frequency can be variable. The dose in the faricimab draft product information is one intravitreal injection every 4 weeks (monthly) for the first 4 doses. Thereafter, based on the physician's judgement of the individual patient's visual and/or anatomic outcomes, faricimab should be administered every 16 weeks (4 months) with some patients requiring dosing at 12-week (3-month) or 8-week (2-month) intervals. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion. It is unclear whether dosing of faricimab will be consistent with a treat-and-extend regimen in clinical practice. Treat-and-extend is the most commonly employed regimen for VEGF inhibitors 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 submission positioned faricimab as an alternative treatment option to standard of care VEGF inhibitors, aflibercept and ranibizumab (see Figure 1). While this appeared reasonable, faricimab is a new treatment and is not currently included in treatment guidelines, and the place in therapy for faricimab is yet to be established. While faricimab has a theoretical advantage of targeting two pathways involved in the pathogenesis of nAMD (VEGF-A and Ang-2), clinical trial evidence presented in the submission was suggestive of similar effectiveness for faricimab and aflibercept for the primary outcome of change from baseline in best corrected visual acuity (BCVA).

Figure 1: Proposed clinical management pathway



Source: Figure 1.7, p21 of the submission

Abbreviations: IVT = intravitreal therapy; VEGF = vascular endothelial growth factor

*Diagnosed by optical coherence tomography or fluorescein angiography (as per PBS criteria)

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

5 Comparator

- 5.1 The submission nominated aflibercept as the main comparator, as aflibercept is the most commonly used VEGF inhibitor for nAMD on the PBS, and is therefore the therapy most likely to be replaced in clinical practice. The submission stated that the nomination of aflibercept as the main comparator can be considered representative of either aflibercept or ranibizumab, as the PBAC has previously accepted non-inferiority between the two agents, and that they should be priced on an injection:injection basis (Therapeutic Relativity Sheets, Ophthalmologicals). Aflibercept is an appropriate main comparator.
- 5.2 Usual dosing of aflibercept for the treatment of nAMD is one 2 mg intravitreal injection per month for three consecutive months, followed by one injection every two months. The treatment interval may be further extended using a treat-and-extend dosing regimen by increasing injection intervals in 2- or 4-weekly increments while maintaining stable visual and/or anatomic outcomes. The aflibercept product information notes that treatment intervals greater than four months (16 weeks) have not been studied.
- 5.3 The submission stated that brolocizumab, listed on the PBS in October 2021 for the treatment of nAMD in patients who are non-responsive to prior anti-VEGF treatment, was not considered a comparator due to its second-line listing. This was reasonable.

- 5.4 Ranibizumab via port delivery system (PDS) was considered by the PBAC in March 2022 for the treatment of patients with nAMD who have responded to prior VEGF inhibitor therapy. The submission argued that, given the requirement for a surgical procedure and assessment of prior response, the place in therapy for ranibizumab PDS is for a niche subset of patients with nAMD. However, given the claimed benefit of reduced injection frequency for both faricimab and ranibizumab PDS compared with existing therapies, ranibizumab PDS may be a potential comparator.
- 5.5 The PBAC accepted the nominated comparator of aflibercept as the main comparator. The PBAC considered that aflibercept could be considered representative of either aflibercept or ranibizumab for the clinical and economic comparisons, as the PBAC has previously accepted noninferiority between the two agents and they are priced on a 1:1 injection basis.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from Macular Disease Foundation Australia and The Royal Australian and New Zealand College of Ophthalmologists via the Consumer Comments facility on the PBS website. Macular Disease Foundation Australia noted the vision loss in patients with nAMD who may experience a range of issues including have burden of treatment with intravitreal injections, high health care burden, high out of pocket costs and access issues, and that about 50% of nAMD patients continue to receive the current treatments beyond 5 years with currently approved treatments. The input from Royal Australian and New Zealand College of Ophthalmologists noted the reduction in treatment burden which was supported by data from TENAYA and LUCERNE clinical trials.

Clinical trials

- 6.3 The submission was based on two ongoing head-to-head trials comparing faricimab to aflibercept (TENAYA, LUCERNE). During the evaluation, two phase 2 trials comparing faricimab with ranibizumab were identified (AVENUE, STAIRWAY). These were not identified in the submission's literature search, which was limited to trials comparing faricimab with the nominated main comparator, aflibercept.
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TENAYA NCT03823287	A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab (RO6867461) in patients with neovascular age-related macular degeneration (nAMD). Heier JS, Kanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials.	Clinical Study Report, May 2021 Lancet January 2022 doi: 10.1016/S0140-6736(22)00010-1. Online ahead of print
LUCERNE NCT03823300	A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab (RO6867461) in patients with neovascular age-related macular degeneration (nAMD). Heier JS, Kanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials.	Clinical Study Report, May 2021 Lancet January 2022 doi: 10.1016/S0140-6736(22)00010-1. Online ahead of print

Source: Table 2.3, p31 of the submission.

Note: Published abstracts of the trials are not presented, given the availability of a full trial publication which was published after lodgement of the submission and identified during the evaluation (Heier et al, 2022).

6.5 The key features of the identically designed TENAYA and LUCERNE trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
TENAYA	671	Randomised, multicentre, double masked, parallel, active comparator-controlled trial. 112 weeks ¹	Low	- Treatment-naïve CNV secondary to AMD (nAMD)	- Change in BCVA - Proportion gaining/avoiding a loss of ≥15 letters in BCVA
LUCERNE	658		Low	- Age ≥50 years - BCVA of 78-24 letters	- Change in CST - Quality of life (NEI VFQ-25) - Adverse events

Source: Section 2.3, p23; Table 2.4, pp34-36; Table 2.7, p40; Table 2.13, p48; Table 2.14, p49 of the submission.

Abbreviations: AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularisation; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; NEI VFQ-25 = National Eye Institute 25-item visual function questionnaire

¹TENAYA and LUCERNE are ongoing trials, with an expected treatment period of approximately 108 weeks, and a final study visit at Week 112. The primary analysis is based on data up to Week 48; with the submission presenting data up to Week 60.

6.6 Baseline characteristics for patients in the TENAYA and LUCERNE trials were generally well-balanced between faricimab and aflibercept treatment arms and across trials (Table 2.8 and Table 2.9 of the submission). The mean age of study participants was 76 years, with 60% female, a mean time since AMD diagnosis of 1.9 months, a mean BCVA of 60 letters, and a mean central subfield thickness (measured between the internal limiting membrane and retinal pigment epithelium) of 357 µm.

6.7 The interventions in the TENAYA and LUCERNE trials are summarised in the table below.

Table 4: Interventions compared in the TENAYA and LUCERNE

Treatment	Dosage regimen ¹	Duration of treatment (weeks) ²	
		TENAYA	LUCERNE
Faricimab	<ul style="list-style-type: none"> • 6 mg intravitreal faricimab every four weeks up to Week 12 (4 injections). • At Week 20, patients with active disease received faricimab every eight weeks. • At Week 24, patients with active disease³ (excluding those with active disease at Week 20) received faricimab every 12 weeks. • Patients without active disease at Week 20 or Week 24 received faricimab every 16 weeks. • From Week 60 to Week 108, patients are to receive treatment according to a personalised treatment interval (between every eight weeks and every 16 weeks), based on central subfield thickness, BCVA, and clinical assessment. 	Mean (SD) Median (range)	Mean (SD) Median (range)
		46.0 (7.9) 48.1 (0-50)	46.4 (6.8) 48.1 (0-50)
Aflibercept	2 mg intravitreal aflibercept every 4 weeks up to Week 8 (3 injections); followed by aflibercept every 8 weeks to Week 104.	47.3 (7.5) 48.1 (0-50)	46.0 (8.1) 48.1 (0-50)

Source: Table 2.11, p47 of the submission; pp45-46 and Table 22, p139 TENAYA clinical study report; pp 45-46 and Table 22, p140 LUCERNE clinical study report.

Abbreviations: BCVA = best corrected visual acuity; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; SD = standard deviation.

¹ To preserve masking, all patients attended study visits every 4 weeks and received sham injections at non-active dosing visits

² At the time of the primary analysis (Week 48; cutoff 5 October, 2020). TENAYA and LUCERNE are ongoing trials, with an expected treatment period of approximately 108 weeks, and a final study visit at Week 112.

³ Active disease was determined by: increase >50 µm in CST compared with the average CST value over the previous two scheduled visits; OR increase ≥75 µm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits; OR decrease ≥5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator); OR decrease ≥10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator); OR presence of new macular haemorrhage (as determined by the investigator), owing to nAMD activity.

6.8 The TENAYA and LUCERNE trials are ongoing. The primary analysis is based on data up to Week 48; with the submission presenting data up to Week 60. The submission did not include any data for the faricimab personalised treatment interval period of the trials (Weeks 60 to 108) as the data are currently unavailable. The Pre-PBAC Response provided follow-up data up to Week 112 from the TENAYA and LUCERNE trials to address concerns regarding the limited long-term efficacy and follow-up data. Data were provided from a presentation reporting Year 2 topline results (April 5, 2022). Updated clinical study reports were not provided. The updated results were not evaluated.

6.9 The clinical study reports for the TENAYA and LUCERNE trials stated that the statistical analysis plan was amended prior to the database snapshot/unmasking to account for COVID-19-related missing data and intercurrent events, with additional supplemental analyses, different missing data handling strategies, and different intercurrent event handling strategies.

6.10 The primary outcome for the TENAYA and LUCERNE trials was the change in BCVA score from baseline. A non-inferiority margin of 4 letters was applied in the

submission, consistent with the pre-specified non-inferiority margin in the TENAYA and LUCERNE trials. The submission noted that a minimal clinically important difference of 5 letters (para 6.12, Ranibizumab Public Summary Document (PSD), March 2018 PBAC meeting) and a non-inferiority margin of 4 letters (para 6.11, Brolucizumab PSD, November 2019 PBAC meeting) were accepted by the PBAC for the treatment of patients with subfoveal choroidal neovascularisation.

- 6.11 The applicability of the TENAYA and LUCERNE trials to the proposed Australian PBS population is uncertain due to differences in dosing (fixed 8-weekly dosing of aflibercept in the trials versus treat-and-extend regimens in clinical practice; faricimab dosing interval based on the presence/absence of active disease at Weeks 20/24 versus personalised dosing according to patient outcomes), monitoring (four-weekly visits versus monitoring based on the patient's status and at the physician's discretion) and differences in the patient population (treatment-naïve patients versus treatment-naïve and treatment-experienced patients on the PBS). The impact of these differences on dosing frequency, comparative effectiveness and safety in clinical practice is uncertain. The submission claimed that the differences in aflibercept dosing are unlikely to have an effect as studies have shown similar outcomes regardless of whether dosing intervals are fixed or treat-and-extend. However, the PBAC noted that there may be differences in comparative safety with less frequent dosing of aflibercept. The PBAC noted the differences between the proposed PBS population and the TENAYA and LUCERNE trials in terms of eligibility criteria, dosing regimens, monitoring frequency and the proportion of patients with prior anti-VEGF treatment, but considered that these differences were unlikely to materially affect the applicability of the trial results to the proposed PBS population.

Comparative effectiveness

- 6.12 The primary outcome of the TENAYA and LUCERNE trials was the mean change from baseline in BCVA averaged over Week 40, Week 44, and Week 48 visits. Updated results based on an average treatment duration of 97-101 weeks were provided in the Pre-PBAC Response. The results of the primary outcome for each of the trials are presented in the table below.

Table 5: Mean change from baseline in BCVA at Weeks 40/44/48 and Weeks 104/108/112 in the TENAYA and LUCERNE trials

	TENAYA			LUCERNE		
	Faricimab Adjusted mean (95% CI)	Aflibercept Adjusted mean (95% CI)	Difference in adjusted means (95% CI)	Faricimab Adjusted mean (95% CI)	Aflibercept Adjusted mean (95% CI)	Difference in adjusted means (95% CI)
Mean change from baseline in BCVA¹						
Primary analysis Weeks 40/44/48	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	0.7 (-1.1, 2.5)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)	0.0 (-1.7, 1.8)
Update: Weeks 104/108/112	3.5	2.8	0.7 (-1.6, 3.0)	4.8	5.1	-0.3 (-2.6, 1.9)

Source: TENAYA and LUCERNE clinical study reports; Faricimab in nAMD TENAYA and LUCERNE Year 2 topline results

Abbreviations: BCVA, best corrected visual acuity; ITT, intention to treat.

Note: ITT population: TENAYA – faricimab N=334, aflibercept N=337; LUCERNE – faricimab N=331, aflibercept N=327

¹Patients with ≥1 non-missing assessment at Weeks 40, 44, 48 (TENAYA – faricimab N=292, aflibercept N=300; LUCERNE – faricimab N=302, aflibercept N=291); at Weeks 104, 108, 112 at Weeks 40, 44, 48 (TENAYA – faricimab N=273, aflibercept N=295; LUCERNE – faricimab N=296, aflibercept N=272), using primary estimand strategy.

²Patients with ≥1 non-missing assessment at Weeks 40, 44, 48 (TENAYA – faricimab N=291, aflibercept N=297; LUCERNE – faricimab N=299, aflibercept N=287); at Weeks 104, 108, 112 (TENAYA – faricimab N=272, aflibercept N=292; LUCERNE – faricimab N=293, aflibercept N=269), using primary estimand strategy.

- 6.13 In the TENAYA and LUCERNE trials, and pooled analysis, the lower limit of the 95% confidence interval of the adjusted mean difference in BCVA between faricimab and aflibercept was greater than -4 ETDRS letters, thereby meeting the pre-specified non-inferiority margin. Results of supportive analyses using alternative handling rules for missing data and/or COVID-19 intercurrent events were consistent with the main analyses. The results for mean change in BCVA score from baseline averaged over Weeks 52, 56 and 60 were consistent with the primary analysis observed over Weeks 40, 44 and 48.
- 6.14 Based on data up to Week 112, the TENAYA and LUCERNE trials continue to demonstrate non-inferiority, as the lower limit of the 95% confidence interval of the adjusted mean difference in BCVA between faricimab and aflibercept was greater than -4 ETDRS letters (the pre-specified non-inferiority margin).
- 6.15 Results of key secondary outcomes for the TENAYA and LUCERNE trials, and pooled analysis, are summarised in the table below.

Table 6: Secondary outcomes in the TENAYA and LUCERNE trials

	Faricimab 6 mg up to Q16W	Aflibercept 2 mg Q8W	Difference
Proportion of patients (95% CI) gaining ≥15 letters of BCVA from baseline at Week 40/44/48			
TENAYA ¹	20.0% (15.6, 24.4)	15.7% (11.9, 19.6)	4.3% (-1.6, 10.1)
LUCERNE ²	20.2% (15.9, 24.6)	22.2% (17.7, 26.8)	-2.0 (-8.3, 4.3)
Pooled ³	20.1% (17.0, 23.2)	19.0% (16.0, 22.0)	1.1% (-3.2, 5.4)
Proportion of patients (95% CI) avoiding a loss of ≥15 letters in BCVA from baseline at Week 40/44/48			
TENAYA ¹	95.4% (93.0, 97.7)	94.1% (91.5, 96.7)	1.3% (-2.2, 4.8)
LUCERNE ²	95.8% (93.6, 98.0)	97.3% (95.5, 99.1)	-1.5% (-4.4, 1.3)
Pooled ³	95.6% (94.0, 97.2)	95.7% (94.1, 97.3)	-0.1% (-2.4, 2.1)
Mean change from baseline (95% CI) in CST at Week 40/44/48			
TENAYA ¹	-136.8 (-142.6, -131.0)	-129.4 (-135.2, -123.5)	-7.4 (-14.7, 0.8)
LUCERNE ²	-137.1 (-143.1, -131.2)	-130.8 (-136.8, -124.8)	-6.4 (-14.8, 2.1)
Pooled ³	-137.0 (-141.2, -132.9)	-130.1 (-134.2, -125.9)	-7.0 (-12.8, -1.1)
Mean change from baseline (95% CI) in CST at Week 104/108/112 (provided in Pre-PBAC Response)			
TENAYA ¹	-146.3	-146.0	-0.3 (-8.8, 8.2)
LUCERNE ²	-151.9	-144.5	-7.5 (-15.6, 0.6)
Mean change from baseline (95% CI) in the NEI VFQ-25 composite score⁴ at Week 48			
TENAYA ¹	4.5 (3.4, 5.7)	2.8 (1.7, 3.9)	1.7 (0.1, 3.3)
LUCERNE ²	4.2 (3.1, 5.3)	5.4 (4.3, 6.6)	-1.2 (-2.8, 0.4)
Pooled ³	4.4 (3.6, 5.2)	4.1 (3.3, 4.9)	0.3 (-0.9, 1.4)

Source: Table 2.17, p57; Table 2.18, p59; Table 2.20, p63; Table 2.21, p66 of the submission. Table 22, p124; Table 23, p126; Table 25, p132 of the Summary of clinical efficacy (provided with the DMO submission)

Abbreviations: BCVA = best corrected visual acuity; CI = confidence interval; CST = central subfield thickness; NEI VFQ-25 = National Eye Institute 25-item visual function questionnaire; Q8W = every 8 weeks; Q16W = every 16 weeks

¹TENAYA trial: N=334 for the faricimab arm; N=337 for the aflibercept arm

²LUCERNE trial: N=331 for the faricimab arm; N=327 for the aflibercept arm

³Pooled TENAYA and LUCERNE trials: N=665 for the faricimab arm; N=664 for the aflibercept arm

⁴Composite scores for the NEI VFQ-25 range from 0 to 100, with higher scores indicating better visual function.

- 6.16 In the TENAYA and LUCERNE trials, the proportions of patients who gained at least 15 letters, and the proportions of patients who avoided a loss of at least 15 letters, from baseline to Week 40/44/48 were comparable between faricimab and aflibercept treatment arms. The results observed from baseline to Week 52/56/60 were comparable to those observed at Week 40/44/48.
- 6.17 Reductions in central subfield thickness from baseline to Week 40/44/48 were numerically larger in the faricimab arm compared with the aflibercept arm in the TENAYA and LUCERNE trials, with the difference between treatment arms in the pooled analysis reaching statistical significance. However, mean change from baseline to Week 52/56/60 showed similar reductions in central subfield thickness between treatment arms. Comparable central subfield thickness reductions were maintained across all treatment arms up to Week 112. Patients treated with faricimab had comparable reductions in CST from baseline at Weeks 104/108/112 to patients treated with aflibercept.
- 6.18 Patients treated with faricimab had a comparable adjusted mean change from baseline in the NEI VFQ-25 composite score at Week 48 compared with patients treated with aflibercept in the TENAYA and LUCERNE trials. Results for NEI VFQ-25 were not reported at Week 60.

6.19 The STAIRWAY and AVENUE trials indicated that faricimab 6 mg at 4-, 8-, 12-and 16-weekly intervals resulted in comparable visual acuity outcomes to ranibizumab 0.5 mg every 4 weeks.

Comparative harms

6.20 A summary of safety outcomes through to Week 48 in the TENAYA and LUCERNE trials is provided in the table below.

Table 7: Safety summary through Week 48 in the TENAYA and LUCERNE trials

	TENAYA		LUCERNE	
	Faricimab N=333	Aflibercept N=336	Faricimab N=331	Aflibercept N=326
Any AE, n (%)	238 (71.5%)	235 (69.9%)	233 (70.4%)	248 (76.1%)
Total AEs, n	858	812	812	846
Serious AEs, n (%)	34 (10.2%)	44 (13.1%)	49 (14.8%)	57 (17.5%)
Total serious AEs, n	47	67	68	122
Deaths, n (%)	5 (1.5%)	1 (0.3%)	4 (1.2%)	7 (2.1%)
AE leading to study w/d, n (%)	3 (0.9%)	4 (1.2%)	5 (1.5%)	6 (1.8%)
AE leading to treatment w/d, n (%)	3 (0.9%)	3 (0.9%)	8 (2.4%)	1 (0.3%)
AE of special interest, n (%)	3 (0.9%)	12 (3.6%)	11 (3.3%)	8 (2.5%)
Ocular adverse events, n (%)				
- Any AE	121 (36.3%)	128 (38.1%)	133 (40.2%)	118 (36.2%)
- Serious AEs	4 (1.2%)	6 (1.8%)	7 (2.1%)	7 (2.1%)
- AE leading to treatment withdrawal	1 (0.3%)	0	5 (1.5%)	1 (0.3%)
- Treatment-related AEs	9 (2.7%)	9 (2.7)	10 (3.0%)	8 (2.5%)
- Treatment-related serious AEs	3 (0.9%)	0	5 (1.5%)	1 (0.3%)
Ocular AEs of special interest, n (%)	3 (0.9%)	6 (1.8%)	5 (1.5%)	6 (1.8%)
- Drop in VA score \geq 30	3 (0.9%)	4 (1.2%)	4 (1.5%)	5 (1.5%)
- Associated with severe intraocular inflammation	0	1 (0.3%)	1 (0.3%)	1 (0.3%)
- Intervention required to prevent permanent vision loss	0	1 (0.3%)	0	0
Adjudicated APTC events	3 (0.9%)	3 (0.9%)	4 (1.2%)	3 (0.9%)
- Non-fatal MI	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
- Non-fatal stroke	0	1 (0.3%)	2 (0.6%)	0
- Death	2 (0.6%)	1 (0.3%)	0	2 (0.6%)

Source: Table 2.23, p70 of the submission; Table 21, pp135-136 of the TENAYA clinical study report; Table 21, pp136-137 of the LUCERNE clinical study report

Abbreviations: AE = adverse event; APTC = Antiplatelet Triallists' Collaboration; VA = visual acuity; w/d = withdrawal

6.21 The incidence of adverse events was similar between the faricimab and aflibercept treatment arms in the TENAYA and LUCERNE trials. The incidence of serious adverse events was numerically higher in the aflibercept arm compared to the faricimab arm of both the TENAYA and LUCERNE trials. The incidence of adverse events leading to study or treatment withdrawal was low. None of the deaths observed in the TENAYA and LUCERNE trials were suspected to be related to the study treatment.

6.22 The most common ocular adverse events were conjunctival haemorrhage, worsening of nAMD, dry eye, and vitreous detachment. The incidence of dry eye was numerically higher in the aflibercept arm compared to the faricimab arm (3.3% versus 2.0%,

respectively). The incidence of vitreous floaters was numerically higher in the faricimab arm compared to the aflibercept arm (3.0% versus 1.7%), as was the incidence of retinal pigment epithelial tear (2.9% versus 1.4%).

- 6.23 The most common non-ocular adverse events were nasopharyngitis, urinary tract infection, hypertension and upper respiratory tract infection. The incidence of falls was numerically higher in the aflibercept arm compared to the faricimab arm (2.9% versus 1.8%, respectively). The incidence of hypertension was numerically higher in the faricimab arm compared to the aflibercept arm (3.6% versus 2.4%, respectively), as was the incidence of arthralgia (3.0% versus 1.7%) and bronchitis (2.6% versus 1.4%).
- 6.24 The incidence of treatment-emergent anti-drug antibodies in faricimab-treated patients was 8.8% in the TENAYA trial and 11.9% in the LUCERNE trial. The trial reports note that, based on the available data, there was no apparent influence of anti-drug antibodies on systemic exposure, overall safety or efficacy.
- 6.25 The Pre-PBAC Response provided updated safety results based on an average treatment duration of 97-101 weeks (see table below). The Pre-PBAC Response stated that no new safety signals were identified, and consistent with the results presented in the submission, the incidence of ocular adverse events and serious ocular adverse events was low and comparable between treatment arms.

Table 8: Safety summary through Week 112 in the TENAYA and LUCERNE trials

	TENAYA		LUCERNE	
	Faricimab N=333	Aflibercept N=336	Faricimab N=331	Aflibercept N=326
Any AE, n (%)	NR	NR	NR	NR
Total AEs, n	1690	1702	1594	1619
Serious AEs, n (%)	NR	NR	NR	NR
Total serious AEs, n	139	157	141	223
Deaths, n (%)	13 (3.9%)	7 (2.1%)	10 (3.0%)	14 (4.3%)
AE leading to study w/d, n (%)	20 (6.0%)	15 (4.5%)	13 (3.9%)	20 (6.1%)
AE leading to treatment w/d, n (%)	12 (3.6%)	9 (2.7%)	16 (4.8%)	9 (2.8%)
AE of special interest, n (%)	16 (4.8%)	23 (6.8%)	24 (7.3%)	20 (6.1%)
Ocular adverse events, n (%)				
- Any AE	183 (55.0%)	190 (56.5%)	175 (52.9%)	155 (47.5%)
- Serious AEs	14 (4.2%)	13 (3.9%)	15 (4.5%)	16 (4.9%)
- AE leading to treatment withdrawal				
- Treatment-related AEs	14 (4.2%)	9 (2.7%)	12 (3.6%)	10 (3.1%)
- Treatment-related serious AEs	4 (1.2%)	0	6 (1.8%)	2 (0.6%)
Ocular AEs of special interest, n (%)	12 (3.6%)	13 (3.9%)	13 (3.9%)	14 (4.3%)
- Drop in VA score \geq 30	9 (2.7%)	10 (3.0%)	9 (2.7%)	10 (3.1%)
- Associated with severe intraocular inflammation	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
- Intervention required to prevent permanent vision loss	2 (0.6%)	2 (0.6%)	2 (0.6%)	3 (0.9%)
Adjudicated APTC events	11 (3.3%)	9 (2.7%)	11 (3.3%)	11 (3.4%)
- Non-fatal MI	1 (0.3%)	2 (0.6%)	2 (0.6%)	1 (0.3%)
- Non-fatal stroke	1 (0.3%)	4 (1.2%)	3 (0.9%)	2 (0.6%)
- Death	9 (2.7%)	3 (0.9%)	7 (2.1%)	8 (2.5%)

Source: Faricimab in nAMD TENAYA and LUCERNE Year 2 topline results

Abbreviations: AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; VA, visual acuity; w/d, withdrawal

6.26 Safety data from the STAIRWAY and AVENUE trials comparing faricimab with ranibizumab were presented in the submission. The safety profile observed in the AVENUE and STAIRWAY trials was consistent with that observed in the TENAYA and LUCERNE trials, with no new or unexpected safety signals observed.

Benefits/harms

6.27 A benefits/harms summary was not presented for faricimab versus aflibercept due to the claim of non-inferiority.

Clinical claim

6.28 The submission described faricimab (6 mg administered up to 16-weekly) as non-inferior to aflibercept (2 mg administered 8-weekly) in terms of effectiveness and safety in patients with nAMD.

6.29 While the clinical claim may be reasonable, the evaluation noted there are applicability issues associated with the TENAYA and LUCERNE trials indicating that trial results may not be generalisable to Australian patients (due to differences in dosing, monitoring, and patient population; see paragraph 6.11).

- 6.30 In addition, the submission claimed that while maintaining similar efficacy outcomes, extended treatment intervals of faricimab (up to 16 weekly) provide a meaningful reduction in the frequency of treatment administration and therefore potentially reduced treatment burden in patients with nAMD compared to aflibercept. This claim was considered uncertain in the evaluation due to the lack of clinical evidence presented comparing faricimab administered according to a personalised treatment interval to aflibercept or ranibizumab administered using a treat-and-extend regimen.
- 6.31 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable and was adequately supported by the data.
- 6.32 In regard to comparative safety, the PBAC noted the incidence of serious adverse events was numerically higher in the aflibercept arm compared to the faricimab arm of both the TENAYA and LUCERNE trials. While the incidence of adverse events in the faricimab and aflibercept treatment arms was numerically similar, adverse events for VEGF inhibitors in clinical practice are likely to depend on the frequency of administration. The PBAC acknowledged that the risk of adverse events with faricimab was low, generally comparable to aflibercept and ranibizumab and was consistent with the established adverse event profile of VEGF inhibitors. The PBAC considered that, on balance, the claim of non-inferior safety was reasonable.

Economic analysis

- 6.33 The submission stated that a cost-minimisation analysis was presented, based on the claim of non-inferior efficacy and safety of faricimab compared with aflibercept. The evaluation noted the analysis would more correctly be described as a cost analysis as the cost-offsets for reduced frequency of treatment administration were not included in the proposed price of faricimab.
- 6.34 The economic analysis presented in the submission was based on published prices.
- 6.35 The (steady state) equi-effective doses proposed in the submission were:
- 4.30 doses of faricimab 6 mg annually is equi-effective to 7.09 doses of aflibercept 2 mg annually.
- 6.36 The cost analysis was conducted over a two-year time horizon to account for differences in costs in the first and subsequent years, due to loading doses.
- 6.37 The submission stated that the average number of faricimab doses in the first year of treatment (6.93) was derived from the average doses in the first 48 weeks of treatment in the TENAYA and LUCERNE trials (6.4 mean administrations through to Week 48, average treatment duration 46.2 weeks), apportioned to a 52-week estimate. The submission's cost minimisation analysis spreadsheet calculated the number of faricimab doses in the first year as 7.20 (6.4 administrations/46.2 weeks average treatment duration × 52 weeks = 7.20) but this value was not used in the cost

analysis. The value used in the submission’s analysis (6.93) was calculated as: 6.4 administrations/48-week trial duration × 52 weeks.

- 6.38 The submission estimated ongoing (second year of treatment onwards) doses for faricimab based on the trial-based proportion of patients on each treatment dosing interval at Week 48 and the average annual number of doses for that treatment interval (see the table below).

Table 9: Participant weighted trial based average number of doses to inform long term dosing

Interval between doses after loading dose phase	Doses	Proportion of patients on each dose interval	
		TENAYA (N=315)	LUCERNE (N=316)
8 weeks	6.5	20%	22%
12 weeks	4.3	34%	33%
16 weeks	3.3	46%	45%
Trial based average number of doses		4.28	4.33
Participant weighted trial based average number of yearly doses		4.30	

Source: Table 3.2, p110 of the submission.

- 6.39 The submission noted that the trial-based dosing did not represent a treat-and-extend regimen, the most commonly used dosing strategy in clinical practice, but the results of the trials did not give any signals that the faricimab patients were undertreated with the trial-based doses. Further, at a population level, the proportion of patients at each interval was considered appropriate to determine the equi-effective dose, and the annual average number of faricimab doses derived using this method was within the recommended doses in the faricimab product information. The trial-based dosing intervals were set at Weeks 20/24 of the trial, determined by the presence/absence of active disease for each patient at that time point; this may not reflect use in clinical practice, where ongoing treatment intervals may be varied based on the patient’s ongoing response to treatment. Although dosing based on personalised treatment intervals was included in the TENAYA and LUCERNE trials between Week 60 and Week 108, results beyond Week 60 were not provided in the submission.
- 6.40 The estimated number of doses per year for aflibercept (8.52 doses per year in year 1, and 7.09 doses per year in year 2) was based on the 2018 DUSC analysis of ranibizumab and aflibercept utilisation (‘Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO’, May 2018 DUSC public release document). The submission noted that the average aflibercept doses per year in the included trials (8 doses in year 1 and 7 doses in year 2) were similar to the DUSC analysis. The 2018 DUSC analysis was based on patients initiating therapy in 2015 and may overestimate the number of doses of VEGF inhibitors in current practice given the increasing use of treat and extend regimens in Australia since the analysis was conducted.
- 6.41 An update to the analysis in the 2018 DUSC report, based on patients who received aflibercept and ranibizumab under AMD authority codes and initiated treatment in 2018 from PBS data was conducted during the evaluation. The mean and median number of aflibercept/ranibizumab doses in the first and second years of treatment

(counted from initiation date) is summarised in the table below. The updated analysis suggests that the average number of scripts per patient in the first year and second year of treatment has decreased for patients initiating treatment in 2015 versus 2018.

Table 10: Average number of intravitreal aflibercept/ranibizumab PBS scripts per year: Patients initiating treatment in 2015 versus 2018

	Patients initiating treatment in 2015		Patients initiating treatment in 2018	
	No. patients	Scripts per year (mean)	No. patients	Scripts per year (mean)
Year 1	7,850	8.52	9,913	7.69
Year 2	6,096	7.09	7,435	6.31

Source: Table 10, p25 DUSC 2018 analysis; Updated analysis provided by the DUSC Secretariat

6.42 The submission requested that the price of each faricimab 6 mg vial would be the same as for aflibercept 2 mg. The following table presents the results of the submission’s cost analysis, based on published DPMQ for aflibercept, and including administration costs for both treatments. A revised cost analysis based on the updated number of scripts per patient from PBS data of aflibercept use conducted during the evaluation is also presented (based on the published AEMP).

Table 11: Results of the cost analysis conducted over a two-year time horizon

	Submission’s approach		Evaluation approach	
	Faricimab	Aflibercept	Faricimab	Aflibercept
	DPMQ \$1,042.95		AEMP \$932.40	
Year 1				
Administration frequency	6.93	8.52	6.93	7.69
Drug cost (DPMQ/AEMP × administration frequency)	\$7,231	\$8,886	\$6,465	\$7,170
Administration cost (\$312.95 ¹ × administration frequency)	\$2,170	\$2,666	\$2,170	\$2,407
Total cost Year 1	\$9,401	\$11,552	\$8,634	\$9,577
Incremental cost Year 1	-\$2,151		-\$942	
Year 2				
Administration frequency	4.30	7.09	4.30	6.31
Drug cost (DPMQ/AEMP × administration frequency)	\$4,488	\$7,395	\$4,012	\$5,883
Administration cost (\$312.95 ¹ × administration frequency)	\$1,347	\$2,219	\$1,347	\$1,975
Total cost Year 2	\$5,834	\$9,613	\$5,359	\$7,858
Incremental cost Year 2	-\$3,779		-\$2,499	
Total cost over 2 years	\$15,235	\$21,166	\$13,993	\$17,435
Incremental cost over 2 years	-\$5,930		-\$3,442	

Source: Cost minimisation analysis spreadsheet; Table 3.7, p.96 of the submission

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

¹Administration costs based on MBS items 42738, 42739, 42740: intravitreal injection of therapeutic substances

6.43 The submission estimated a net saving of \$5,930 for faricimab compared to aflibercept over a two-year time horizon (\$15,235 versus \$21,166). It is likely that the net cost savings attributed to faricimab have been overestimated, as the analysis is highly dependent on the use of faricimab and aflibercept in practice:

- Average doses of aflibercept per year may vary from the submission’s estimates, particularly if the proportion of patients maintained on treat-and-extend regimens has increased in recent years. This was reflected in the updated PBS data in which the average number of intravitreal aflibercept and ranibizumab injections in the first and second years of treatment decreased. Using the updated data, the incremental cost savings over two years reduced from \$5,930 (base case) to \$3,442.
 - Trial-based dose intervals for faricimab were determined based on patients’ active disease status at Week 20/24 only. It is unclear whether this would be representative of use in clinical practice.
 - There were limited clinical trial data available beyond one year of therapy.
 - The draft product information for faricimab states that monitoring between dosing visits should be scheduled based on the patient’s status and at the physician’s discretion. No additional monitoring costs were included in the submission’s cost analysis.
- 6.44 The ESC requested the sponsor provide the results of the cost analysis using 7.20 doses of faricimab in the first year. The Pre-PBAC Response stated that a sensitivity analysis was provided within the cost-minimisation analysis based on 7.20 faricimab doses in the first year which shows consistent outcomes and a comparable level of savings with the initial analysis (based on 6.93 doses), however, the results were not reported in the Pre-PBAC Response. A revised cost analysis using 7.20 doses of faricimab in the first year and the updated PBS data of aflibercept use is shown below (based on the published AEMP).

Table 12: Updated results of the cost analysis conducted over a two-year time horizon using 7.20 doses of faricimab in the first year and the updated PBS data of aflibercept use

	Submission's approach		Evaluation approach	
	Faricimab	Aflibercept	Faricimab	Aflibercept
	DPMQ \$1,042.95		AEMP \$932.40	
Year 1				
Administration frequency	7.20	8.52	7.20	7.69
Drug cost (DPMQ/AEMP × administration frequency)	\$7,513	\$8,886	\$6,717	\$7,170
Administration cost (\$312.95 ¹ × administration frequency)	\$2,254	\$2,666	\$2,254	\$2,407
Total cost Year 1	\$9,767	\$11,552	\$8,971	\$9,577
Incremental cost Year 1	-\$1,785		-\$606	
Year 2				
Administration frequency	4.30	7.09	4.30	6.31
Drug cost (DPMQ/AEMP × administration frequency)	\$4,488	\$7,395	\$4,012	\$5,883
Administration cost (\$312.95 ¹ × administration frequency)	\$1,347	\$2,219	\$1,347	\$1,975
Total cost Year 2	\$5,834	\$9,613	\$5,359	\$7,858
Incremental cost Year 2	-\$3,779		-\$2,499	
Total cost over 2 years	\$15,602	\$21,166	\$14,330	\$17,435
Incremental cost over 2 years	-\$5,564		-\$3,105	

Source: Cost minimisation analysis spreadsheet

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

¹Administration costs based on MBS items 42738, 42739, 42740: intravitreal injection of therapeutic substances

- 6.45 Using 7.20 doses in the first year instead of 6.93 reduces the incremental savings associated with faricimab versus aflibercept from -\$5,930 to -\$5,564 in the submission's base case; and from -\$3,442 to -\$3,105 using the evaluation approach. The PBAC considered using 7.20 doses in the first year instead of 6.93 was the more reasonable approach.
- 6.46 A patient perspective analysis, incorporating out-of-pocket costs to patients including PBS patient co-payments and average gap fees paid after MBS benefits was presented in Section 3.3.2 of the submission. The submission noted that 70% of patients typically pay \$224 out-of-pocket (gap fee for specialist visit after MBS benefit applied) per administration for intravitreal injections (Department of Health Medical Cost Finder, 2021), and the average PBS patient co-payment is \$12.92 per script. Based on the patient perspective analysis, faricimab was expected to save patients approximately \$742 over the two-year time horizon, compared to aflibercept.
- 6.47 The submission presented the results of sensitivity analyses based on alternative time horizons (5 and 10 years), dose relativities (25%/50% higher doses, no difference in doses), and trial-based dosing. The submission noted that the results were cost-saving in all scenarios, apart from the scenario assuming no difference in faricimab and aflibercept dose frequency, which was cost neutral. The estimated savings in the submission may not be realised in clinical practice if the average annual number of injections for faricimab is similar to aflibercept or ranibizumab.

6.48 In response to concerns regarding uncertainty in equi-effective doses, the Pre-PBAC Response noted that further follow-up data from the clinical trials indicate a higher proportion of patients on a 16-weekly dose at Week 112 (63%) than at Week 48 (45%), and suggested that the weighted trial-based average number of yearly doses would likely be lower than that used in the submission. The Pre-PBAC Response noted that, while uncertainty in equi-effective doses exists, all economic scenario analyses presented in the submission and commentary were cost saving; and out of pocket implications for patients were also cost saving.

Drug cost/patient/year

6.49 The drug cost per patient for faricimab is \$7,231 in the initial year of treatment (based on the proposed published DPMQ of \$1,042.95 × 6.93 administrations), and \$4,488 in each subsequent year (based on the proposed published DPMQ of \$1,042.95 × 4.30 administrations). Based on the updated cost analysis for faricimab versus aflibercept using 7.20 doses for faricimab, the drug cost per patient for faricimab is \$7,509.24 in the initial year of treatment (based on the proposed published DPMQ of \$1,042.95 × 7.20 administrations), and \$4,484.69 in each subsequent year (based on the proposed published DPMQ of \$1,042.95 × 4.30 administrations).

6.50 The drug cost per patient for aflibercept is \$8,886 in the initial year of treatment (based on the published DPMQ of \$1,042.95 × 8.52 administrations), and \$7,395 in each subsequent year (based on the published DPMQ of \$1,042.95 × 7.09 administrations). Based on the updated DUSC Secretariat analysis, the drug cost per patient for aflibercept is \$8,020 in the initial year of treatment (based on the published DPMQ of \$1,042.95 × 7.69 administrations) and \$6,581 in each subsequent year (based on the published DPMQ of \$1,042.95 × 6.31 administrations).

Estimated PBS usage & financial implications

6.51 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial implications of a PBS listing for faricimab. The financial implications presented in the submission were based on published prices. Key inputs are summarised below.

Table 13: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Current market			
Total aflibercept and ranibizumab scripts 2020	415,059	PBS utilisation data from 2020 calendar year (ranibizumab 10 mg/mL PBS item numbers 1382R and 10138N and aflibercept PBS item numbers 2168D and 12152N)	This was reasonable.
% AMD that is nAMD	87% Aflibercept and ranibizumab scripts for AMD in 2017 divided by	DUSC report: Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO: DUSC, May 2018.	The proportion used by the submission would more accurately be described as the proportion of total aflibercept and ranibizumab prescriptions that were for

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Data	Value	Source	Comment
	the sum of AMD and RVO scripts.	Proportion applied to PBS utilisation data from 1 July 2015 for ranibizumab and 1 October 2015 for aflibercept, to 1 May 2020 (when macular oedema secondary to retinal vein occlusion was split to separate item numbers) to derive the PBS market for nAMD from 2015 to 2020.	the treatment of AMD (excluding prescriptions for treatment of RVO).
Projected growth in PBS scripts for nAMD	Yr 1: 7.78% Yr 2: 6.79% Yr 3: 6.56% Yr 4: 5.45% Yr 5: 5.20% Yr 6: 5.64%	PBS data for ranibizumab 10 mg/mL (PBS item numbers 1382R and 10138N) and aflibercept (PBS item numbers 2168D and 12152N) from January 2015 to December 2020. Projected utilisation based on PBS scripts for ranibizumab and aflibercept for nAMD from 2020, extrapolated with linear trend using least squares method	The submission assumed that PBS listing of faricimab will not increase the eligible market size. This assumption was considered uncertain.
Treatment utilisation			
Faricimab uptake rate	Yr 1: 45% Yr 2: 50% Yr 3: 55% Yr 4: 60% Yr 5: 60% Yr 6: 60%	Assumption, based on the sponsor's internal estimates.	Estimated uptake is highly uncertain and likely overestimated and may differ in clinical practice.
Number of scripts per year (aflibercept and ranibizumab)	7.09	DUSC 2018 report on ranibizumab and aflibercept utilisation; average number of injections in Year 2 of therapy for patients initiating treatment in 2015.	The updated PBS data (see Economic analysis section) demonstrates that the number of scripts/year for ranibizumab and aflibercept has decreased over time from the estimates used in the submission.
Number of scripts per year (faricimab)	4.30	Derived from the distribution of patients between Q8W, Q12W and Q16W dosing intervals at Week 48 in the TENAYA and LUCERNE trials.	Trial based estimates were based on the presence/absence of active disease at Weeks 20/24, which may not reflect use in the Australian setting.
Script substitution rate	0.61 (=4.30/7.09)	Based on the equi-effective doses proposed in the submission for Year 2 onward. Calculated as 4.30 faricimab administrations / 7.09 aflibercept/ranibizumab administrations.	The scripts per year used in the financial estimates were based on use in second and subsequent years. The substitution rate will be different for the initial year of therapy.

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Data	Value	Source	Comment
Costs			
Faricimab	\$1,042.95	Requested price (published)	-
Aflibercept, ranibizumab	\$1,042.95	Published DPMQ	-
Patient co-payment	\$12.92	2020 calendar year PBS utilisation data for ranibizumab and aflibercept was used to calculate the proportional PBS/RPBS co-payments.	This was reasonable. Weighted average co-payment calculated during the evaluation based on the PBS/RPBS split (94.31% versus 5.69%, respectively) and co-payment amounts (\$13.31 PBS and \$6.45 RPBS).
MBS costs	Fee: \$312.95 80% benefit: \$250.36	MBS items 42738/42739 (paracentesis of anterior chamber or vitreous cavity or both); item 42740 (intravitreal injection of therapeutic substances when performed in conjunction with other intraocular surgery).	This was reasonable.

Source: Table 4.3, p120 of the submission.

Abbreviations: AMD = age-related macular degeneration; DPMQ = dispensed price for maximum quantity; nAMD = neovascular age-related macular degeneration; RVO = retinal vein occlusion; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks.

6.52 The estimated utilisation and financial impact of listing faricimab presented in the submission are summarised below.

Table 14: Estimated use and financial implications

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Estimated ranibizumab scripts	¹	¹	¹	²	²	²
Estimated aflibercept scripts	²	²	³	³	³	³
Estimated total scripts	⁴	⁴	⁵	⁵	⁵	⁵
Faricimab uptake rate	45%	50%	55%	60%	60%	60%
Faricimab scripts (substituted scripts x 0.61)	¹	¹	¹	¹	²	²
Cost to PBS/RPBS	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁷	\$ ⁷	\$ ⁷
Less patient co-payments	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸
Total net cost to PBS/RPBS	\$⁶	\$⁶	\$⁶	\$⁷	\$⁷	\$⁷
Displaced ranibizumab scripts	⁹	¹⁰	¹	¹	¹	¹
Displaced aflibercept scripts	¹	¹	¹	¹	²	²
Total displaced scripts	²	²	²	³	³	³
Offsets to PBS/RPBS	-\$ ⁷	-\$ ⁷	-\$ ⁷	-\$ ¹¹	-\$ ¹¹	-\$ ¹¹
Less patient co-payments	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸
Net offsets to PBS/RPBS	-\$⁷	-\$⁷	-\$⁷	-\$¹¹	-\$¹¹	-\$¹¹
Net cost to PBS/RPBS	-\$¹²	-\$¹³	-\$⁶	-\$⁶	-\$⁶	-\$⁶
MBS costs faricimab	\$ ¹³	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶
MBS cost offsets ranibizumab/aflibercept	-\$ ⁶	-\$ ⁶	-\$ ⁷	-\$ ⁷	-\$ ⁷	-\$ ⁷
Net cost to MBS	-\$¹⁴	-\$¹⁵	-\$¹²	-\$¹³	-\$¹³	-\$⁶
Overall Net cost to Gov't	-\$⁶	-\$⁶	-\$⁶	-\$⁷	-\$⁷	-\$⁷

Source: Table 4.5, p122; Table 4.6, p122; Table 4.7, p122; Table 4.10, p124; Table 4.13, p126; Table 4.14, p127; Table 4.17, p129 of the submission; Section 4 workbook

The redacted values correspond to the following ranges:

¹100,000 to < 200,000

²200,000 to < 300,000

³300,000 to < 400,000

⁴400,000 to < 500,000

⁵500,000 to < 600,000

⁶\$100 million to < \$200 million

⁷\$200 million to < \$300 million

⁸\$0 to < \$10 million

⁹70,000 to < 80,000

¹⁰90,000 to < 100,000

¹¹\$300 million to < \$400 million

¹²\$80 million to < \$90 million

¹³\$90 million to < \$100 million

¹⁴\$50 million to < \$60 million

¹⁵\$60 million to < \$70 million

6.53 Based on the published prices of aflibercept and ranibizumab, the net cost savings of listing faricimab for nAMD on the PBS/RPBS was estimated to be \$80 million to < \$90 million in Year 1, increasing to savings of \$100 million to < \$200 million in Year 6, a cumulative savings of \$600 million to < \$700 million over the first 6 years of listing. When additional savings from reduced MBS administration costs were added, the net cost savings to Government were estimated to be \$100 million to < \$200 million in Year 1, increasing to savings of \$200 million to < \$300 million in Year 6, a cumulative savings of > \$1 billion over the first 6 years of listing.

6.54 The evaluation noted the estimated cost savings are dependent on the assumed administration frequencies and may not be realised if the administration frequencies differ in clinical practice. Adjusted estimates derived during the evaluation based on the updated PBS data (6.31 scripts per patient for aflibercept and ranibizumab) are summarised below. The adjustment resulted in lower estimated cost savings to PBS/RPBS of \$60 million to < \$70 million in Year 1, increasing to savings of \$100 million to < \$200 million in Year 6, a cumulative savings of \$500 million to < \$600 million over the first 6 years of listing. Incorporation of reduced costs to MBS resulted in an overall net cost savings to Government of \$900 million to < \$1 billion over 6 years.

Table 15: Adjusted estimated use and financial impact of a PBS/RPBS listing for faricimab (published DPMQ) using updated PBS data of aflibercept scripts/year

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Projected ranibizumab scripts	¹	¹	¹	²	²	²
Projected aflibercept scripts	²	²	³	³	³	³
Projected total scripts	⁴	⁴	⁵	⁵	⁵	⁵
Faricimab uptake rate	45%	50%	55%	60%	60%	60%
Faricimab scripts (substituted scripts x 0.68)	¹	¹	¹	²	²	²
Cost to PBS/RPBS	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁷	\$ ⁷	\$ ⁷
Less patient co-payments	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸	-\$ ⁸
Total net cost to PBS/RPBS	\$⁶	\$⁶	\$⁶	\$⁷	\$⁷	\$⁷

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	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Displaced ranibizumab scripts	- ⁹	- ¹⁰	- ¹	- ¹	- ¹	- ¹
Displaced aflibercept scripts	- ¹	- ¹	- ¹	- ¹	- ²	- ²
Total displaced scripts	- ²	- ²	- ²	- ³	- ³	- ³
Offsets to PBS/RPBS	-\$ ⁷	-\$ ⁷	-\$ ⁷	-\$ ¹¹	-\$ ¹¹	-\$ ¹¹
Less patient co-payments	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸
Net offsets to PBS/RPBS	-\$⁷	-\$⁷	-\$⁷	-\$¹¹	-\$¹¹	-\$¹¹
Net cost to PBS/RPBS	-\$¹²	-\$¹³	-\$¹⁴	-\$⁶	-\$⁶	-\$⁶
MBS costs faricimab	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶
MBS cost offsets ranibizumab/aflibercept	-\$ ⁶	-\$ ⁶	-\$ ⁷	-\$ ⁷	-\$ ⁷	-\$ ⁷
Net cost to MBS	-\$¹⁵	-\$¹⁶	-\$¹²	-\$¹³	-\$¹⁷	-\$¹⁷
Overall Net cost to Gov't	-\$⁶	-\$⁶	-\$⁶	-\$⁶	-\$⁶	-\$⁷

Source: Calculated during the evaluation using updated PBS data of average scripts/year for aflibercept and ranibizumab.

The redacted values correspond to the following ranges:

- ⁹100,000 to < 200,000
- ¹⁰200,000 to < 300,000
- ¹¹300,000 to < 400,000
- ¹²400,000 to < 500,000
- ¹³500,000 to < 600,000
- ⁶\$100 million to < \$200 million
- ⁷\$200 million to < \$300 million
- ⁸\$0 to < \$10 million
- ⁹70,000 to < 80,000
- ¹⁰90,000 to < 100,000
- ¹¹\$300 million to < \$400 million
- ¹²\$60 million to < \$70 million
- ¹³\$70 million to < \$80 million
- ¹⁴\$90 million to < \$100 million
- ¹⁵\$40 million to < \$50 million
- ¹⁶\$50 million to < \$60 million
- ¹⁷\$80 million to < \$90 million

6.55 The PBAC considered the submission’s assumption of 45% uptake of faricimab in Year 1 was overestimated. Based on market growth of 8-10%, and assuming that all new patients would begin treatment on faricimab, an uptake of 45% would require approximately one-third of patients already on VEGF inhibitor therapy to switch to faricimab. The PBAC noted that while faricimab has a theoretical advantage of targeting two pathways involved in the pathogenesis of nAMD, it has a higher dose frequency and clinical trial evidence was suggestive of similar effectiveness for faricimab and aflibercept. Given this, the PBAC considered that it is unclear whether patients who are currently receiving treatment with aflibercept/ranibizumab would switch to faricimab. The PBAC considered that a market uptake rate of approximately 20% would be a reasonable assumption for Year 1. The PBAC considered the proposed cost savings with listing faricimab to be highly speculative and may not be realised in practice. Additionally, the financial impacts did not account for loading dose requirements in the initial year of treatment with faricimab which would further reduce the assumed cost savings to Government. The ESC noted the uptake of

faricimab could also be potentially impacted if the ranibizumab PDS was available (see paragraph 5.4).

- 6.56 The submission provided a range of sensitivity analyses based on the equi-effective doses and the annualised growth rate. The submission noted that the primary source of uncertainty in the financial estimates is the script equivalence for existing standard of care, but that cost savings to Government were maintained in all scenarios except when the equi-effective dose of faricimab was equivalent to aflibercept, which results in a neutral budget impact.

Quality Use of Medicines

- 6.57 No quality use of medicines issues were raised in the submission.

Financial Management – Risk Sharing Arrangements

- 6.58 A risk sharing arrangement (RSA) was not proposed. The submission noted that an RSA currently exists that represents a shared expenditure cap across ranibizumab, aflibercept and brolocizumab intravitreal injections. The PBAC considered that given the uncertainty of the estimates and that the anti-VEGF therapies on the PBS are managed via a RSA, it would be appropriate to apply the same arrangements to faricimab were it to list as well.

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 faricimab for the treatment of neovascular age-related macular degeneration (nAMD). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of faricimab would be acceptable if it were cost-minimised to PBS-listed anti-VEGF treatments such as aflibercept and ranibizumab for the same indication.
- 7.2 The PBAC supported a 2-year time horizon for the cost-minimisation calculation, and considered the equi-effective doses to be:
- Year 1: 7.20 doses of faricimab annually to 7.69 doses of aflibercept 2 mg annually
 - Year 2: 4.30 doses of faricimab annually to 6.31 doses of aflibercept 2 mg annually.

The PBAC accepted the faricimab administration frequency based on an analysis of faricimab administration frequency from the TENAYA and LUCERNE trials, where the first year of treatment was derived from the average doses in the first 48 weeks of treatment in the TENAYA and LUCERNE trials (6.4 mean administrations through to Week 48, average treatment duration 46.2 weeks), apportioned to a 52-week estimate

while ongoing treatment was based on the trial-based average number of yearly doses for faricimab across different treatment intervals at Week 48; and the aflibercept administration frequency was based on PBS data.

- 7.3 The PBAC considered aflibercept to be the appropriate main comparator. The PBAC considered that aflibercept could be considered representative of either aflibercept or intravitreal ranibizumab for the clinical and economic comparisons, as the PBAC has previously accepted noninferiority between the two agents and they are priced on a 1:1 injection basis.
- 7.4 The PBAC noted the differences between the proposed PBS population and the TENAYA and LUCERNE trials in terms of eligibility criteria, dosing regimens, monitoring frequency and the proportion of patients with prior anti-VEGF treatment, but considered that these differences were unlikely to materially affect the applicability of the trial results to the proposed PBS population.
- 7.5 The PBAC considered that the non-inferior efficacy of faricimab compared to aflibercept was established. The PBAC noted that there was no statistically significant difference in the primary or secondary endpoints between the faricimab and aflibercept arms in either the TENAYA and LUCERNE trials. The PBAC also noted that the nominated non-inferiority margin of 4 letters was met, and that this margin had previously been accepted by the PBAC in the treatment of patients with subfoveal choroidal neovascularisation (paragraph 6.11, brolocizumab PSD, November 2019), was met.
- 7.6 The PBAC noted that the incidence of serious adverse events was numerically higher in the aflibercept arm compared to the faricimab arm of both the TENAYA and LUCERNE trials, however the incidence of adverse events was similar between the faricimab and aflibercept treatment arms in the TENAYA and LUCERNE trials. The PBAC noted that adverse events for VEGF inhibitors in clinical practice are likely to be dependent on the frequency of administration. The Pre-PBAC Response stated that no new safety signals were identified, and consistent with the results presented in the submission, the incidence of ocular adverse events and serious ocular adverse events was low and comparable between treatment arms. The PBAC acknowledged that the risk of adverse events with faricimab was low, generally comparable to aflibercept and ranibizumab and was consistent with the established adverse event profile of VEGF inhibitors. The PBAC considered that, on balance, the claim of noninferior safety was reasonable. The Pre-PBAC Response provided follow-up data from the TENAYA and LUCERNE trials up to Week 112 to address concerns regarding the limited long-term efficacy and follow-up data. Data were provided from a presentation reporting Year 2 topline results (April 5, 2022). The updated results were not evaluated. Overall, the PBAC considered that the results in terms of overall efficacy and safety were consistent with the primary analysis for the TENAYA and LUCERNE trials provided in the original submission.

- 7.7 The PBAC accepted the market share approach to estimate the financial impact of listing faricimab on the PBS for nAMD. However, the PBAC considered the assumption that faricimab would account for 45% of the market share in Year 1 of listing was unrealistically high, as it is unclear whether patients currently receiving treatment with aflibercept/ranibizumab would switch to faricimab. The PBAC considered 20% of market share in Year 1 to be a more reasonable assumption. The PBAC also noted that the Sponsor had assumed there would be no growth in the market resulting from the listing of faricimab on the PBS, and that no allowance was made for loading doses in the initial year of treatment in patients who have switched from aflibercept to faricimab.
- 7.8 The PBAC considered the proposed cost savings with listing faricimab to be highly speculative, in particular noting that the cost savings estimated in the submission depend on the assumed dose frequencies, which may not be realised if dose frequencies differ in clinical practice. The PBAC also noted that additional costs to Government may be incurred if the dose frequency for faricimab is higher than aflibercept, particularly in the first 2 years of listing due the faricimab loading doses in patients who switching from aflibercept to faricimab. The PBAC considered that there should be no extra cost to Government given the PBAC's acceptance of the faricimab administration frequency based on average doses in the first 48 weeks of treatment in the TENAYA and LUCERNE trials (6.4 mean administrations through to Week 48, average treatment duration 46.2 weeks), apportioned to a 52-week estimate, and the aflibercept administration frequency was based on the PBS data for aflibercept.
- 7.9 The PBAC considered that it would be appropriate for faricimab join the Deed arrangements in place for ranibizumab, aflibercept and brolucizumab intravitreal injections in CNV due to AMD with no increase in expenditure caps to ensure the listing resulted in no additional cost.
- 7.10 The PBAC noted the requested listing and considered that 2 repeats would be appropriate for faricimab for all treatment phases. The PBAC noted that this was consistent with aflibercept and ranibizumab, which are used under treat-and-extend regimens.
- 7.11 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."
- 7.12 The PBAC advised that faricimab should be included as a prior treatment in the initial and grandfather restriction of brolucizumab for subfoveal choroidal neovascularisation (CNV). The PBAC noted that this change would make brolucizumab a second-, third-, or fourth-line treatment in this indication. The PBAC recalled that brolucizumab was previously accepted as a subsequent therapy after aflibercept or

ranibizumab and considered that this would also apply to faricimab (paragraph 7.4, brolocizumab PSD, March 2021 PBAC meeting). The PBAC considered that upon listing of faricimab for nAMD, the restriction flow-on change should apply to the following brolocizumab initial and grandfather restriction: “Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of treatment with: 1. Aflibercept and/or 2. Ranibizumab and/or 3. Faricimab.”

- 7.13 The PBAC advised, under Section 101 (4AACD) of the *National Health Act*, that faricimab 0.24 mL injection vial and faricimab 0.2 mL injection syringe should be considered equivalent for the purposes of substitution (i.e., ‘a’ flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution).
- 7.14 The PBAC advised, under Section 101(3BA) of the *National Health Act*, that faricimab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.15 The PBAC advised that faricimab 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 faricimab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over aflibercept, 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	No. of Rpts	Available brands
FARICIMAB					
<i>faricimab</i> 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	2	Vabysmo
<i>faricimab</i> 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	2	Vabysmo
Category / Program: GENERAL – General Schedule (Code GE)					

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	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required –Written
	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 on the same authority prescription form.
	Administrative Advice: Pharmaceutical benefits that have the form faricimab 0.24 mL injection vial and pharmaceutical benefits that have the form faricimab 0.2 mL injection syringe are equivalent for the purposes of substitution.
	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
	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 Instructions: Authority approval for initial treatment of each eye must be sought.
	Prescribing Instructions: The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report.
	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 authority to prescribe should 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

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	2	Vabysmo

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faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	2	Vabysmo
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical					
Restriction type: <input checked="" type="checkbox"/> Authority Required – (STREAMLINED)					
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					
AND					
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 been granted an authority prescription for the same eye					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	2	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	2	Vabysmo
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Written					
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					
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:					
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
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 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Prescribing Instructions: The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report.

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

Roche welcomes the PBAC's decision to recommend faricimab for the treatment of patients with neovascular age-related macular degeneration.

Roche are working with the Department of Health towards a PBS listing at the earliest opportunity.