5.01 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, General Schedule listing of faricimab for the treatment of patients with visual impairment due to diabetic macular oedema (DMO).

1.2 Listing was requested on the basis of a cost-minimisation approach versus aflibercept, as a proxy for PBS-listed vascular endothelial growth factor (VEGF) inhibitors.

1.3 A concurrent parallel process submission for faricimab for the treatment of neovascular age-related macular degeneration was considered at the May 2022 intracycle PBAC meeting.

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

Component	Description
Population	Patients with visual impairment due to diabetic macular oedema (DMO)
Intervention	Faricimab intravitreal injection
Comparator	Aflibercept intravitreal injection (as a proxy for PBS-listed VEGF inhibitors aflibercept and ranibizumab)
Outcomes	Best corrected visual acuity (BCVA); proportion with a ≥2 step improvement in EDTRS diabetic retinopathy severity score; proportion gaining ≥15 EDTRS letters; change in central subfield thickness; proportion with absence of diabetic macular oedema; quality of life; ocular and non-ocular adverse events.
Clinical claim	In patients with DMO, faricimab is as effective as aflibercept at maintaining BCVA with fewer injections and a comparable safety profile.

Source: Table 1.1, p2 of the submission.
Abbreviations: EDTRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor.

2 Background

Registration status

2.1 The submission was submitted under the TGA/PBAC parallel process. 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
- DMO.

2.3 Faricimab was approved for use by the US Food and Drug Administration on 28 January 2022 for the treatment of patients with DMO and nAMD. 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 DMO. Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	~~5~~*3*	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	~~5~~*3*	Vabysmo
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required ~~- Telephone~~ *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: 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				
	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: Authority approval for initial treatment of each eye must be sought. 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 Diabetic Macular Oedema (DMO) - 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**	**№.of Rpts**	**Available brands**
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	*NEW*	1	1	~~5~~*1*	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	*NEW*	1	1	~~5~~*1*	Vabysmo
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical				
	Restriction type: ☒Authority Required – ~~Telephone~~ *(STREAMLINED)*				
	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: 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
		AND
		Clinical criteria:
		Patient must have previously been issued with an authority prescription for this drug 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

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	*NEW*	1	1	~~5~~0	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	*NEW*	1	1	~~5~~0	Vabysmo

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical
	Restriction type: ☒Authority Required – Written
	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
	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:
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	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 Diabetic Macular Oedema (DMO) - PBS Supporting Information Form; and* *c) a copy of the optical coherence tomography or fluorescein angiogram report.*

3.2 The submission proposed a special pricing arrangement, with a published dispensed price for faricimab of $1,042.95, and an effective price matching the aflibercept effective price (which is not known to the sponsor). The proposed published price is the same as the proposed published price for faricimab requested in the nAMD submission.

3.3 The proposed restriction is narrower than the indication proposed in the draft product information, which does not limit treatment based on the presence/level of visual impairment, method of diagnosis, or to use as monotherapy (+/- laser photocoagulation).

3.4 There were differences between the proposed restriction and the eligibility criteria for the RHINE/YOSEMITE trials. The RHINE/YOSEMITE trials recruited patients with a higher level of visual impairment (best corrected visual acuity (BCVA) of 73 to 25 Early Treatment Diabetic Retinopathy Study (ETDRS) letters versus 78 to 39 ETDRS letters in the proposed restriction). Patients were also required to have a documented diagnosis of diabetes mellitus (Type 1 or Type 2) with current regular use of oral or injectable

anti-hyperglycaemic agents and a HbA1c of ≤10% in the prior 2 months. The RHINE/YOSEMITE trials also included explicit baseline central subfield thickness (CST) requirements (CST ≥325 µm by Spectralis SD-OCT or ≥315 µm by Cirrus SD-OCT or Topcon SD-OCT). The Pre-PBAC response acknowledged the difference in BCVA requirements between the RHINE/YOSEMITE trial eligibility criteria and the proposed PBS restriction. The Pre-PBAC Response noted that the proposed BCVA of 78 to 39 letters is consistent with the aflibercept and ranibizumab PBS restrictions and argued that the difference between the RHINE/YOSEMITE trial inclusion criteria and the PBS restriction is unlikely to have an impact, given that subgroup analyses suggest that baseline BCVA is not a treatment effect modifier. The PBAC considered that the faricimab listing should be consistent with the restrictions for aflibercept and ranibizumab for the above criteria.

3.5 The submission requested grandfathering provisions for patients who initiate treatment with faricimab prior to the PBS listing date. The submission stated that an estimate of eligible grandfathered patients could be provided if faricimab receives a positive PBAC recommendation. The PBAC noted that given the small number of Australian patients who participated in the clinical trials (19 patients treated with faricimab in the RHINE 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.

3.6 The requested authority for initiating patients was Authority Required – Telephone was inconsistent with the current restrictions for initiating patients for aflibercept and ranibizumab which are Authority Required – Written. 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 proposed a maximum of 5 repeats for faricimab, consistent with the listings of nominated comparators aflibercept and ranibizumab. While 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 Pre-PBAC Response argued that inclusion of a lower number of repeats for faricimab as suggested by the Secretariat may result in additional administrative burden for

specialist clinicians. The PBAC considered that 5 repeats would be appropriate for faricimab for all treatment phases to maintain consistency with aflibercept and ranibizumab listings for DMO, noting some patients receive these medicines under treat-and-extend regimens.

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).

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. Symptoms of macular oedema include blurring or distortion of central vision, and disturbance in the perception of colours. Untreated macular oedema may lead to permanent loss of central vision. The prevalence of DMO is expected to grow due to the increasing prevalence of diabetes.

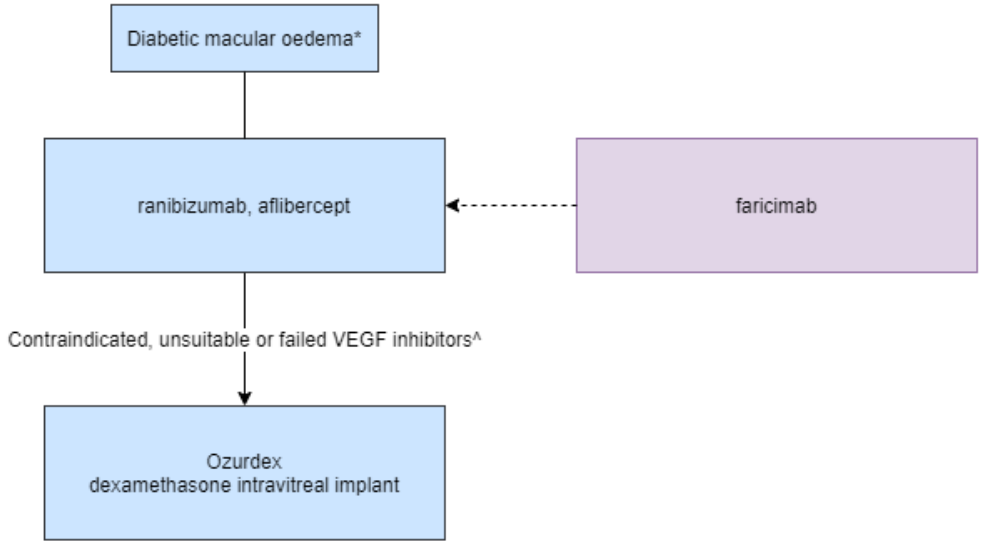
4.2 The current standard of care for patients with DMO is intravitreal administration of anti-vascular endothelial growth factor (VEGF) therapy. VEGF is a growth factor which stimulates growth of new vessels in the eye and is a key driver of the vascular leakage associated with DMO. Two anti-VEGF intravitreal therapies (aflibercept and ranibizumab) are currently listed on the PBS for the treatment of DMO.

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. Angiopoietin-2 is upregulated in the eyes of patients with diabetes and is associated with vascular leakage and inflammation. The recommended dose for faricimab is 6 mg administered by intravitreal injection every four weeks (monthly) for the first four 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.

4.4 The submission positioned faricimab as an alternative to PBS-listed VEGF inhibitors ranibizumab and aflibercept (see Figure 1). While this appeared reasonable, faricimab 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 DMO (VEGF-A and angiopoietin-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 BCVA.

Figure 1: Proposed clinical management algorithm



Source: Figure 1.7, p19 of the submission
Abbreviations: VEGF = vascular endothelial growth factor.
*Diagnosed by optical coherence tomography or fluorescein angiography (as per PBS criteria).
^Patient must have had a cataract removed OR patient must be scheduled for cataract surgery (in the treated eye).
Note: Treatment must be as monotherapy; OR the treatment must be in combination with laser photocoagulation. To be PBS treatment eligible, 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.

4.5 The submission claimed that treatment with faricimab is associated with a reduction in administration frequency compared to aflibercept/ranibizumab, potentially reducing the treatment burden for patients with DMO. This claim was considered uncertain, as PBS utilisation data for aflibercept and ranibizumab indicated a decline in annual aflibercept/ranibizumab administrations among patients who initiated treatment in 2018, consistent with a trend toward use of treat-and-extend regimens.

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

5 Comparator

5.1 The submission nominated aflibercept as the main comparator. The main arguments provided in support of this nomination were:

- Aflibercept 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 there were 60,902 aflibercept and 21,602 ranibizumab PBS dispensings in 2020.
- Given the PBAC's prior conclusion of non-inferiority between aflibercept and ranibizumab, aflibercept can be considered representative of available anti-VEGF

therapies (paragraph 7.2, aflibercept, Public Summary Document (PSD), November 2019 PBAC meeting).

5.2 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 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.

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 Diabetes Australia via the Consumer Comments facility on the PBS website. Macular Disease Foundation Australia noted that patients with DMO are often of working age and experience a range of issues including a high health care burden, high out of pocket costs and access issues, and that persistence with the current PBS-listed treatment options drops to less than 50% by year 3. Diabetes Australia provided general support for the submission.

Clinical trials

6.3 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
RHINE (NCT03622593)	Phase III, multicentre, randomised, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab in patients with diabetic macular edema.	RHINE clinical study report, May 2021.
	Eter N, Lin H, Abreu F, Ruiz CQ, Willis JR et al. Design and rationale of the YOSEMITE and RHINE trials: Two phase 3 studies of faricimab in patients with diabetic macular edema.	*Investig. Ophthalmol. Vis. Sci.* 2021; Conference: ARVO 62(8).
	Wells JA, Lin H, Haskova Z, Willis JR et al. Efficacy, durability, and safety of faricimab in diabetic macular edema (DME): One year results from the phase 3 YOSEMITE and RHINE trials.	*Investig. Ophthalmol. Vis. Sci.* 2021; Conference: ARVO 62(8).
	Wykoff CC, Abreu F, Adamis, AP, Basu K et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials	*The Lancet 2022; 399(10326):741-755.*
YOSEMITE (NCT03622580)	A Phase III, multicentre, randomised, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab (RO6867461) in patients with diabetic macular edema.	YOSEMITE clinical study report, May 2021
	Eter N, Lin H, Abreu F, Ruiz CQ, Willis JR et al. Design and rationale of the YOSEMITE and RHINE trials: Two phase 3 studies of faricimab in patients with diabetic macular edema.	*Investig. Ophthalmol. Vis. Sci.* 2021; Conference: ARVO 62(8).
	Wells JA, Lin H, Haskova Z, Willis JR et al. Efficacy, durability, and safety of faricimab in diabetic macular edema (DME): One year results from the phase 3 YOSEMITE and RHINE trials.	*Investig. Ophthalmol. Vis. Sci.* 2021; Conference: ARVO 62(8).
	Wykoff CC, Abreu F, Adamis, AP, Basu K et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials	*The Lancet 2022; 399(10326):741-755.*

Source: Table 2.3, p29 of the submission.
Abbreviations: ARVO = Association for Research in Vision and Ophthalmology.
Italicised publication identified during the evaluation.

6.4 The submission was based on two head-to-head trials (RHINE; YOSEMITE) comparing faricimab 8-weekly or faricimab administered based on a personalised treatment interval (PTI), to aflibercept 8-weekly.

6.5 The key features of the RHINE and YOSEMITE 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
RHINE	951	Randomised, multi-centre, double-masked, parallel, active comparator-controlled trial (100 weeks)[1]	*Low*	• Adults with macular thickening secondary to DMO involving the centre of the fovea • BCVA of 73 to 25 letters • Type 1 or 2 diabetes with current regular use of oral or injectable anti-diabetic medications and HbA1c ≤10% • Prior VEGF inhibitor use (20%) or VEGF inhibitor treatment naïve (80%)	• Change in BCVA (primary) • ≥2-step improvement on the ETDRS DRS • Dose frequency distribution in PTI arm • Proportion gaining ≥15 letters in BCVA • Change in CST • Proportion with absence of DMO • Quality of life (NEI VFQ-25 composite score) • Adverse events
YOSEMITE	940		*Low*		

Source: Section 2.3.1, pp31-32; Table 2.4, pp33-34; Table 2.7, pp38-39; Table 2.12, p48; Table 2.13, p49 of the submission.
Abbreviations: BCVA = best corrected visual acuity; CST = central subfield thickness; DMO = diabetic macular oedema; DRS = diabetic retinopathy severity; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated haemoglobin; NEI VFQ-25 = National Eye Institute Visual Functioning Questionaire-25; PTI = personalised treatment interval; VEGF = vascular endothelial growth factor.
[1] The trials are ongoing with a planned treatment duration of 96 weeks and a follow-up visit at Week 100.

6.6 The RHINE and YOSEMITE trials are ongoing, international, randomised trials, conducted concurrently with identical eligibility, treatment protocols, and outcomes. The submission was based on the results of the primary analysis for the RHINE and YOSEMITE trials, which was conducted at a mean duration of follow-up of approximately 53 weeks. Treatment is planned to continue for a total of 96 weeks with a final follow-up visit scheduled for Week 100. The evaluation noted that patients who complete the RHINE and YOSEMITE trials will be eligible to participate in an open-label extension study evaluating the long-term safety and tolerability of faricimab (Rhone-X study). In its Pre-PBAC Response, the final clinical study reports for the RHINE and YOSEMITE trials were made available. These reported outcomes based on a mean treatment duration of 90 weeks in the RHINE trial and 88 weeks in the YOSEMITE trial. Due to the scope of the final clinical study report documents, the full results for the RHINE and YOSEMITE trials were not evaluated.

6.7 The trials recruited adults with macular thickening secondary to DMO involving the centre of the fovea. Participants were required to have visual impairment (BCVA of 73 to 25 letters), be on regular oral or injectable anti-diabetic medications for Type 1 or 2 diabetes and have a HbA1c of ≤10%. The RHINE and YOSEMITE trials included patients with prior intravitreal anti-VEGF therapy use (approximately 20% of recruited patients) as well as treatment naïve patients.

6.8 Baseline characteristics for patients in the RHINE and YOSEMITE trials were generally well balanced across the three treatment arms. The mean age of study participants was 62 years, with approximately 60% male subjects, a mean time since diagnosis of 19 months, a mean BCVA of 62 letters, and a mean central subfield thickness (CST) of 480 µm.

6.9 Each trial included three treatment arms as described in the table below. All three treatment arms undertook 4-weekly study visits.

Table 4: Interventions compared in the RHINE and YOSEMITE trials

Treatment	Dosage regimen	Mean duration of treatment, weeks (SD)[1]
RHINE and YOSEMITE		
Faricimab 8-weekly	Faricimab 6 mg intravitreal injection every 4 weeks to Week 20, followed by faricimab 6 mg intravitreal injection every 8 weeks from Week 24 to Week 96.	RHINE: 53.1 (10.0) YOSEMITE: 53.1 (9.8)
Faricimab PTI	Faricimab 6 mg intravitreal injection every 4 weeks to at least Week 12, followed by faricimab 6 mg based on personalised treatment interval from Week 16 to Week 96.	RHINE: 54.5 (7.5) YOSEMITE: 52.9 (10.4)
Aflibercept 8-weekly	Aflibercept 2 mg intravitreal injection every 4 weeks to Week 16, followed by aflibercept 2 mg every 8 weeks from Week 20 to Week 96.	RHINE: 53.7 (8.7) YOSEMITE: 53.2 (9.5)

Source: Table 2.11, p46; Table 2.21, p67 of the submission.
Abbreviation: NR = not reported; PTI = personalised treatment interval; SD = standard deviation.
[1] Submission based on primary analysis at approximately 53 weeks. Trials are ongoing with a planned treatment duration of 96 weeks and with a follow-up visit at Week 100.

6.10 A minimum of two investigators were required per site to fulfill the masking requirements of the study. At least one investigator was not blinded to the assigned treatment and performed study treatments. At least one investigator designated as the assessor physician was masked to each patient's treatment assignment and conducted ocular assessments. To preserve the randomised treatment arm masking, a sham procedure involving the blunt end of an empty syringe being pressed against the anesthetised eye was undertaken during visits where no intravitreal injection was scheduled.

6.11 The primary outcome for the RHINE and YOSEMITE trials was the change in BCVA score from baseline, based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. Analyses were pre-specified for the ITT population as well as the anti-VEGF treatment naïve population. The primary outcome was assessed using a 3-step hierarchical testing procedure: non-inferiority of faricimab compared to aflibercept 8-weekly in the ITT population with a non-inferiority margin of 4 letters; superiority of faricimab compared with aflibercept 8-weekly in the treatment naive population; superiority of faricimab compared to aflibercept 8-weekly in the ITT population.

6.12 A non-inferiority margin of 4 letters was nominated in the submission, consistent with the pre-specified non-inferiority margin applied in the clinical trials. The submission noted that a non-inferiority margin of 4 letters for this outcome was previously accepted by the PBAC in the treatment of patients with subfoveal choroidal neovascularisation (paragraph 6.11, brolucizumab PSD, November 2019 PBAC meeting).

6.13 The proportion of patients with a ≥2-step diabetic retinopathy severity improvement from baseline at Week 52 was a key secondary endpoint for the RHINE and YOSEMITE trials. A non-inferiority margin of 10% was pre-specified for this outcome in the RHINE and YOSEMITE trials.

6.14 The clinical study reports for the RHINE and YOSEMITE 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.

6.15 The submission claimed that the population and circumstances of use in the RHINE and YOSEMITE trials are applicable to the Australian clinical setting. However, there were differences between the proposed PBS population and the RHINE/YOSEMITE trials in terms of eligibility criteria (visual impairment severity, HbA1c requirement), dosing regimens (fixed 8-week dosing for aflibercept in the trial versus treat-and-extend treatment in Australian clinical practice), monitoring frequency (four-weekly visits versus monitoring based on the patient's status and at the physician's discretion), and the proportion of patients with prior anti-VEGF treatment (approximately 20% in the trial; unclear proportion in the PBS population). The evaluator considered the impact of these differences on dosing frequency, comparative effectiveness and safety in clinical practice is uncertain.

6.16 The Pre-PBAC Response acknowledged differences between the 8-weekly aflibercept treatment regimen used in the RHINE and YOSEMITE trials and the likely use of VEGF inhibitor treat-and-extend regimens in clinical practice but argued that there is nothing to suggest that patient outcomes would differ based on fixed dosing versus treat-and-extend regimens. However, the PBAC noted that there may be differences in comparative safety with less frequent dosing of aflibercept. The Pre-PBAC Response also argued that differences in monitoring frequency between the clinical trial setting (based on protocol-defined visit frequency) and in clinical practice (based on the patient's status and at the physician's discretion) are unlikely to have an effect on treatment outcomes. The PBAC noted the differences between the proposed PBS population and the RHINE/YOSEMITE 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

6.17 The results for the RHINE and YOSEMITE primary outcome, change in BCVA score from baseline averaged over Weeks 48/52/56, are presented in the table below. The Pre-PBAC Response presented pooled results for the RHINE and YOSEMITE trials for the primary outcome of change from baseline in BCVA which reported outcomes based on a mean treatment duration of 90 weeks in the RHINE trial and 88 weeks in the YOSEMITE trial.

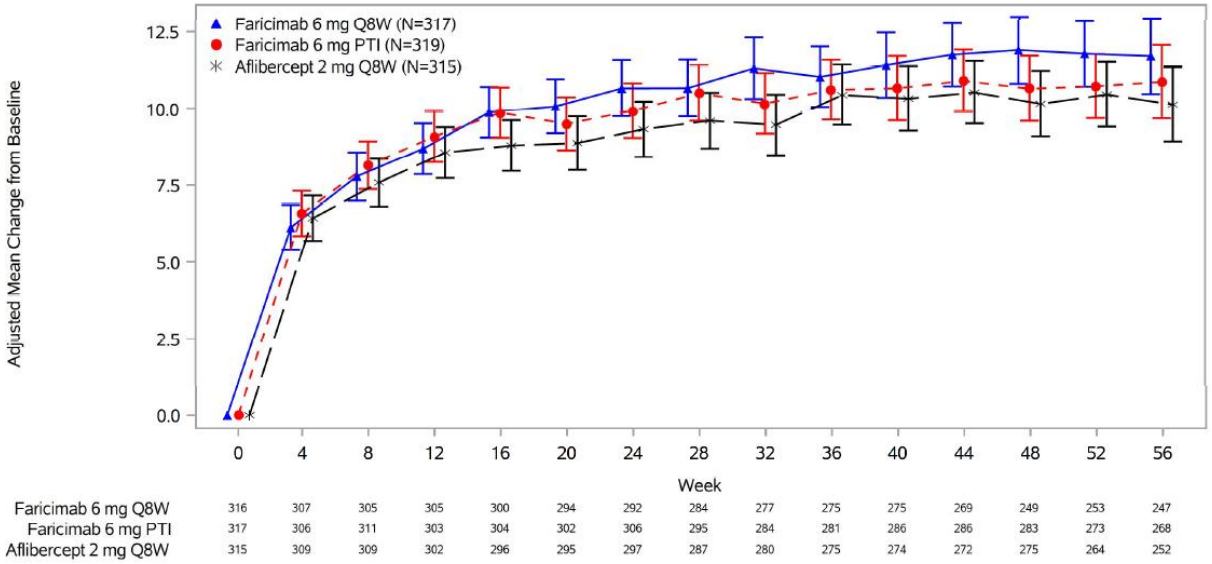
Table 5: Change from baseline in BCVA averaged over Weeks 48, 52 and 56 (ITT population; primary outcome)

Trial	FARI 8-weekly, adjusted mean letters	FARI PTI, adjusted mean letters	AFLI 8-weekly, adjusted mean letters	FARI 8-weekly vs AFLI 8-weekly, difference	FARI PTI vs AFLI 8-weekly, difference
Primary analysis (97.5% CI)					
RHINE	N=317 11.8 (10.6, 13.0)	N=319 10.8 (9.6, 11.9)	N=315 10.3 (9.1, 11.4)	1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)
YOSEMITE	N=315 10.7 (9.4, 12.0)	N=313 11.6 (10.3, 12.9)	N=312 10.9 (9.6, 12.2)	-0.2 (-2.0, 1.6)	0.7 (-1.1, 2.5)
Pooled estimate[1]	N=632 11.2 (10.5, 12.0)	N=632 11.2 (10.4, 11.9)	N=627 10.5 (9.8, 11.3)	0.7 (-0.4, 1.7)	0.6 (-0.4, 1.7)
Final analysis (95% CI)					
RHINE	N=317 10.9 (9.5, 12.3)	N=319 10.1 (8.7, 11.5)	N=315 9.4 (7.9, 10.8)	1.5 (-0.5, 3.6)	0.7 (-1.3, 2.7)
YOSEMITE	N=315 10.7 (9.4, 12.1)	N=313 10.7 (9.4, 12.1)	N=312 11.4 (10.0, 12.7)	-0.7 (-2.6, 1.2)	-0.7 (-2.5, 1.2)
Pooled estimate[1]	N=632 10.8 (9.8, 11.8)	N=632 10.4 (9.4, 11.4)	N=627 10.3 (9.3, 11.3)	0.5 (-0.9, 1.8)	0.1 (-1.3, 1.5)

Source: Table 2.14, p53 of the submission; Table 2, p4 of the faricimab pre-PBAC response; Table 6, p71 of the RHINE final clinical study report; Table 6, p74 of the YOSEMITE final clinical study report.
Abbreviations: AFLI = aflibercept; BCVA = best corrected visual acuity; CI = confidence interval; FARI = faricimab; ITT = intention to treat.
[1] Pooled estimate including RHINE and YOSEMITE trials.

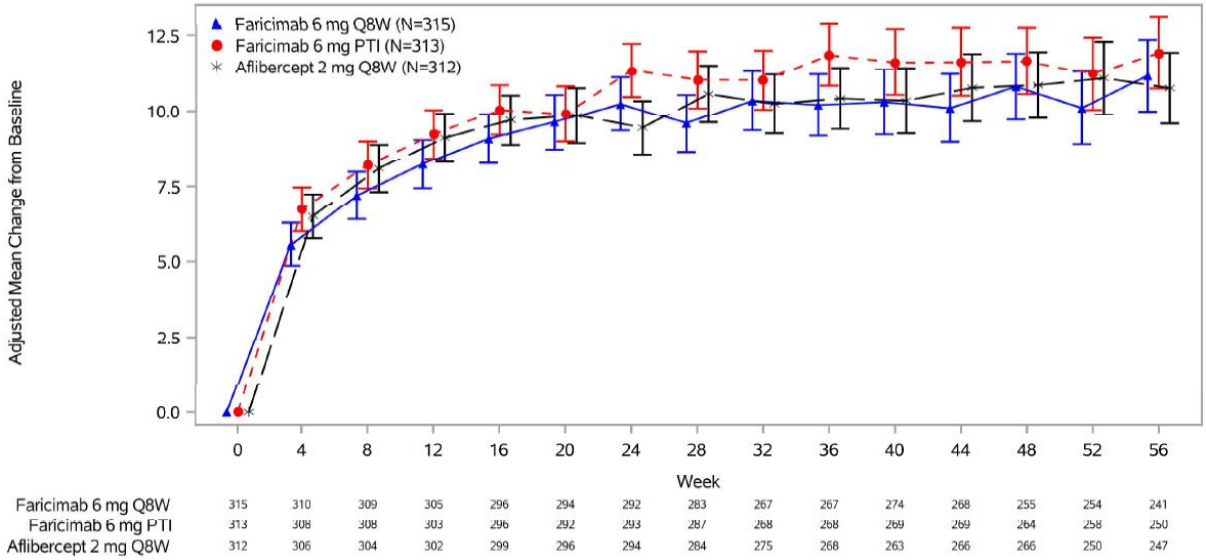
6.18 Results for the change in BCVA score over time are presented below.

Figure 2: Change from baseline in BCVA in the through Week 56 (RHINE trial, ITT)



Source: Figure 5, p120 of the RHINE clinical study report.
Abbreviations: BCVA = best corrected visual acuity; ITT = intention-to-treat; PTI = personalised treatment interval; Q8W = 8-weekly.

Figure 3: Change from baseline in BCVA in the through Week 56 (YOSEMITE trial, ITT)



Source: Figure 5, p119 of the YOSEMITE clinical study report.
Abbreviations: BCVA = best corrected visual acuity; ITT = intention-to-treat; PTI = personalised treatment interval; Q8W = 8-weekly.

6.19 There was no statistically significant difference for the change in BCVA from baseline between the faricimab 8-weekly arm and aflibercept 8-weekly arms, or between the faricimab PTI and the aflibercept 8-weekly arms, for the RHINE trial, YOSEMITE trial, or the pooled RHINE/YOSEMITE comparison. The results met the nominated non-inferiority margin of 4 letters. Results of supportive analyses using alternative handling rules for missing data and/or COVID-19 intercurrent events were consistent with the main analyses.

6.20 Results for the treatment naïve subgroup were generally consistent with the ITT results. Patients treated with faricimab 8-weekly or PTI did not achieve a superior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept 8-weekly. Based on the hierarchical testing procedure for the RHINE and YOSEMITE trials, all subsequent hypotheses for the primary endpoint were considered negative.

6.21 Results of secondary outcomes for the ITT population are presented in the table below.

Table 6: Key efficacy and quality of life outcomes for the RHINE and YOSEMITE trials (ITT population)

Trial[1]	FARI 8-weekly	FARI PTI	AFLIB 8-weekly	FARI 8-weekly vs AFLI 8-weekly, difference	FARI PTI vs AFLI 8-weekly, difference
Proportion with a ≥2-step DRS improvement on the ETDRS DRS score at Week 52, weighted % (97.5% CI)					
RHINE[1]	44.2 (37.1, 51.4)	43.7 (36.8, 50.7)	46.8 (39.8, 53.8)	-2.6 (-12.6, 7.4)	-3.5 (-13.4, 6.3)
YOSEMITE[2]	46.0 (38.8, 53.1)	42.5 (35.5, 49.5)	35.8 (29.1, 42.5)	10.2 (0.3, 20.0)	6.1 (-3.6, 15.8)
Pooled estimate[3]	45.1 (40.1, 50.1)	43.1 (38.2, 48.0)	41.3 (36.5, 46.2)	3.8 (-3.2, 10.8)	1.2 (-5.7, 8.1)
Proportion who gained ≥15 EDTRS letters at Week 48/52/56, weighted % (95% CI)					
RHINE[1]	33.8 (28.4, 39.2)	28.5 (23.6, 33.3)	30.3 (25.0, 35.5)	3.5 (-4.0, 11.1)	-2.0 (-9.1, 5.2)
YOSEMITE[2]	29.2 (23.9, 34.5)	35.5 (30.1, 40.9)	31.8 (26.6, 37.0)	-2.6 (-10.0, 4.9)	3.5 (-4.0, 11.1)
Pooled estimate[3]	31.5 (27.7, 35.3)	31.9 (28.3, 35.6)	31.0 (27.3, 34.7)	0.5 (-4.8, 5.8)	0.7 (-4.4, 5.9)
Proportion who avoided a loss of ≥15 EDTRS letters at Week 48/52/56, weighted % (95% CI)					
RHINE[1]	98.9 (97.6, 100.0)	98.7 (97.4, 100.0)	98.6 (97.2, 99.9)	0.3 (-1.6, 2.1)	0.0 (-1.8, 1.9)
YOSEMITE[2]	98.1 (96.5, 99.7)	98.6 (97.2, 100.0)	98.9 (97.6, 100.0)	-0.8 (-2.8, 1.3)	-0.3 (-2.2, 1.5)
Pooled estimate[3]	98.5 (97.5, 99.5)	98.6 (97.7, 99.6)	98.7 (97.8, 99.6)	-0.3 (-1.6, 1.1)	-0.1 (-1.5, 1.2)
Change from baseline in CST, adjusted mean µm (95% CI)					
RHINE[1]	-196 (-204, -188)	-188 (-196, -180)	-170 (-178, -162)	-25.7 (-37.4, -14.0)	-17.6 (-29.2, -6.0)
YOSEMITE[2]	-207 (-215, -198)	-197 (-205, -188)	-170 (-179, -162)	-36.2 (-47.8, -24.7)	-26.2 (-37.7, -14.7)
Pooled estimate[3]	-201 (-207, -195)	-192 (-198, -187)	-170 (-176, -164)	-30.7 (-38.9, -22.5)	-22.2 (-30.3, -14.0)
Proportion with absence of DMO (CST <325 µm) at one year, weighted % (95% CI)					
RHINE[1]	85.5 (81.3, 89.7)	81.5 (77.1, 85.9)	73.2 (68.0, 78.3)	12.3 (5.7, 18.9)	8.2 (1.5, 14.9)
YOSEMITE[2]	81.3 (76.8, 85.9)	78.0 (73.1, 82.8)	65.4 (59.9, 70.8)	16.0 (8.9, 23.1)	12.7 (5.4, 20.0)
Pooled estimate[3]	83.4 (80.3, 86.5)	79.8 (76.5, 83.0)	69.3 (65.5, 73.0)	14.1 (9.3, 19.0)	10.4 (5.5, 15.4)
Change from baseline in NEI VFQ-25 composite score at Week 52, adjusted mean (95% CI)[4]					
RHINE[1]	6.9 (5.5, 8.2)	7.0 (5.7, 8.2)	7.6 (6.3, 8.9)	-0.7 (-2.6, 1.1)	-0.6 (-2.5, 1.2)
YOSEMITE[2]	7.6 (6.3, 9.0)	7.9 (6.6, 9.3)	7.8 (6.4, 9.2)	-0.2 (-2.1, 1.7)	0.1 (-1.8, 2.1)
Pooled estimate[3]	7.3 (6.3, 8.2)	7.4 (6.5, 8.4)	7.7 (6.7, 8.6)	-0.4 (-1.8, 0.9)	-0.2 (-1.6, 1.1)

Source: Table 2.15, p55; Table 2.17, pp57-58; Table 2.18, p61; Table 2.19, p63; Table 2.20, p65 of the submission.

Abbreviations: AFLIB = aflibercept; CI = confidence interval; CST = central subfield thickness; DMO = diabetic macular oedema; DRS = diabetic retinopathy severity; EDTRS = Early Treatment Diabetic Retinopathy Study; FARI = faricimab; NEI VFQ-25 = National Eye Institute Visual Functioning Questionaire-25; PTI = personalised treatment interval.

[1] RHINE trial: N=317 for faricimab 8-weekly arm; N=319 for faricimab PTI arm; N=315 for aflibercept 8-weekly arm.

[2] YOSEMITE trial: N=315 for faricimab 8-weekly arm; N=313 for faricimab PTI arm; N=312 for aflibercept 8-weekly arm.

[3] Pooled estimate of RHINE and YOSEMITE trials. N=632 for faricimab 8-weekly arm; N=632 for faricimab PTI arm; N=627 for aflibercept 8-weekly arm.

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

6.22 There was no statistically significant difference between faricimab (8-weekly or PTI) and aflibercept 8-weekly for the proportion of patients with a ≥2 step improvement on the ETDRSS DRSS, the proportion who gained ≥15 EDTRS letters, the proportion who avoided a loss of ≥15 EDTRS letters, or the change from baseline in the NEI VFQ-25 composite score.

6.23 The proportion of patients with a ≥2 step improvement on the ETDRSS diabetic retinopathy severity score was a key secondary outcome of the RHINE and YOSEMITE trials. While the results for the YOSEMITE trial and the pooled RHINE/YOSEMITE estimate met the pre-specified non-inferiority margin of 10%, the lower 97.5% confidence intervals for the RHINE trial comparisons exceeded 10%.

6.24 A statistically significant difference in favour of faricimab (8-weekly and PTI) was observed for the change from baseline in central subfield thickness (CST) and the

proportion of patients with absence of DMO (based on a CST <325 µm). The submission did not nominate a non-inferiority margin or minimal clinically important difference for this outcome.

Comparative harms

6.25 A summary of pooled safety outcomes for the RHINE and YOSEMITE trials to Week 56 is presented in the table below.

Table 7: Pooled safety outcomes for the RHINE and YOSEMITE trials to Week 56

	Faricimab 8-weekly N=630	Faricimab PTI N=632	Aflibercept 8-weekly N=625
Any AE, n (%)	513 (81.4)	486 (76.9)	488 (78.1)
Total AEs, n	2169	1891	1852
Serious AEs, n (%)	419 (23.7)	126 (19.9)	114 (18.2)
Total serious AEs, n	272	193	191
Deaths, n (%)	13 (2.1)	9 (1.4)	9 (1.4)
AE leading to study withdrawal, n (%)	16 (2.5)	12 (1.9)	9 (1.4)
AE leading to treatment withdrawal, n (%)	10 (1.6)	12 (1.9)	7 (1.1)
AE of special interest, n (%)	27 (4.3)	26 (4.1)	13 (2.1)
Ocular adverse events, n (%) - Any AE - Serious AEs, n (%) - AE leading to treatment withdrawal - Treatment-related AEs - Treatment-related serious AEs	 235 (37.3) 15 (2.4) 2 (0.3) 19 (3.0) 0	 225 (35.6) 19 (3.0) 8 (2.3) 16 (2.5) 5 (0.8)	 215 (34.4) 8 (1.3) 2 (0.3) 19 (3.0) 0
Ocular AEs of special interest, n (%) • Drop in visual acuity score ≥30 • Associated with severe intraocular inflammation • Intervention required to prevent permanent vision loss	15 (2.4) 8 (1.3) 3 (0.5) 5 (0.8)	17 (2.7) 8 (1.3) 5 (0.8) 5 (0.8)	6 (1.0) 3 (0.5) 1 (0.2) 2 (0.3)
Adjudicated APTC events, n (%) - Non-fatal myocardial infarction - Non-fatal stroke - Death	13 (2.1) 4 (0.6) 4 (0.6) 5 (0.8)	12 (1.9) 2 (0.3) 4 (0.6) 6 (0.9)	14 (2.2) 6 (1.0) 4 (0.6) 4 (0.6)

Source: Table 2.22, pp69-70; Table 2.23, p73 of the submission.
Abbreviations: AE = adverse event; APTC = Antiplatelet Triallists' Collaboration; PTI = personalised treatment interval.

6.26 Treatment with faricimab 8-weekly was associated with a numerically higher incidence and total number of treatment-emergent adverse events compared to the faricimab PTI and aflibercept 8-weekly arms. The most common treatment emergent adverse events in the faricimab arms (incidence ≥2%) were conjunctival haemorrhage, cataract, vitreous detachment, vitreous floaters, intraocular pressure increase, dry eye, eye pain, and cortical cataract.

6.27 Treatment with faricimab 8-weekly was also associated with a numerically higher incidence and total number of serious adverse events compared to the faricimab PTI and aflibercept 8-weekly arms.

6.28 Death occurred in 2.1% of patients in the faricimab 8-weekly arm, 1.4% of patients in the faricimab PTI arm, and 1.4% of patients in the aflibercept 8-weekly arm. None of the reported deaths were deemed to be related to study treatment.

6.29 Treatment with faricimab 8-weekly and PTI was associated with numerically higher adverse events of special interest compared to the aflibercept 8-weekly arm, predominantly due to a higher number of patients experiencing a drop in visual acuity score of ≥30 letters.

6.30 The incidence of treatment-emergent anti-drug antibodies was 6.9% in faricimab-treated patients in the RHINE trial and 10.0% in the YOSEMITE trial. The trial reports stated that, based on the available data, there was no apparent influence of anti-drug antibodies on systemic exposure, overall safety or efficacy.

6.31 The Pre-PBAC response presented pooled results for the RHINE and YOSEMITE trials for ocular adverse events through to Week 100, which were derived from the 'Summary of Clinical Safety Update' and the 'Summary of Clinical Efficacy Update', which were not provided by the Sponsor. Individual summaries of adverse event results for the RHINE and YOSEMITE trials are presented in the table below.

Table 8: Comparison of safety outcomes for the RHINE and YOSEMITE trials at the final analysis

	RHINE trial			YOSEMITE trial		
	Faricimab 8-weekly N=317	Faricimab PTI N=319	Aflibercept 8-weekly N=314	Faricimab 8-weekly N=313	Faricimab PTI N=313	Aflibercept 8-weekly N=311
Mean treatment duration, weeks (SD)	88.5 (21.1)	91.6 (15.9)	89.3 (19.2)	87.6 (21.5)	88.2 (22.0)	88.5 (20.6)
Any AE, n (%)	283 (89.3)	272 (85.3)	274 (87.3)	290 (92.7)	286 (91.4)	277 (89.1)
Total AEs, n	1658	1420	1386	1621	1632	1476
Serious AEs, n (%)	97 (30.6)	82 (25.7)	100 (31.8)	111 (35.5)	117 (37.4)	93 (29.9)
Total serious AEs, n	173	152	189	234	201	174
Deaths, n (%)	12 (3.8)	9 (2.8)	10 (3.2)	16 (5.1)	21 (6.7)	13 (4.2)
AE leading to study withdrawal, n (%)	16 (5.0)	14 (4.4)	16 (5.1)	22 (7.0)	27 (8.6)	18 (5.8)
AE leading to treatment withdrawal, n (%)	7 (2.2)	9 (2.8)	5 (1.6)	8 (2.6)	9 (2.9)	5 (1.6)
AE of special interest, n (%)	24 (7.6)	23 (7.2)	20 (6.4)	19 (6.1)	22 (7.0)	15 (4.8)
Ocular adverse events, n (%)						
- Any AE	166 (52.4)	165 (51.7)	140 (44.6)	147 (47.0)	146 (46.6)	144 (46.3)
- Serious AEs, n (%)	14 (4.4)	20 (6.3)	13 (4.1)	12 (3.8)	14 (4.5)	7 (2.3)
- AE leading to treatment withdrawal	1 (0.3)	6 (1.9)	1 (0.3)	4 (1.3)	6 (1.9)	1 (0.3)
- Treatment-related AEs	10 (3.2)	14 (4.4)	15 (4.8)	10 (3.2)	7 (2.2)	6 (1.9)
- Treatment-related serious AEs	0	3 (0.9)	0	0	4 (1.3)	0
Ocular AEs of special interest, n (%)	14 (4.4)	20 (6.3)	12 (3.8)	11 (3.5)	13 (4.2)	8 (2.6)
- Drop in visual acuity score ≥30	10 (3.2)	16 (5.0)	9 (2.9)	8 (2.6)	7 (2.2)	7 (2.3)
- Associated with severe intraocular inflammation	1 (0.3)	0	1 (0.3)	2 (0.6)	5 (1.6)	0
- Intervention required to prevent permanent vision loss	3 (0.9)	4 (1.3)	3 (1.0)	3 (1.0)	4 (1.3)	1 (0.3)
Adjudicated APTC events, n (%)	11 (3.5)	8 (2.5)	14 (4.5)	23 (7.3)	22 (7.0)	18 (5.8)
- Non-fatal myocardial infarction	3 (0.9)	1 (0.3)	3 (1.0)	4 (1.3)	4 (1.3)	4 (1.3)
- Non-fatal stroke	3 (0.9)	4 (1.3)	4 (1.3)	8 (2.6)	6 (1.9)	7 (2.3)
- Death	5 (1.6)	3 (0.9)	7 (2.2)	11 (3.5)	12 (3.8)	7 (2.3)

Source: Table 23, p149; Table 24 p154 of the RHINE final clinical study report; Table 23, p150; Table 24, p155 of the YOSEMITE final clinical study report.

Abbreviations: AE = adverse event; APTC = Antiplatelet Triallists' Collaboration; PTI = personalised treatment interval.

6.32 Based on the updated safety data for the RHINE and YOSEMITE trials, treatment with faricimab 8-weekly was associated with a numerically higher incidence and total number of treatment-emergent adverse events compared to the faricimab PTI and aflibercept 8-weekly arms. While treatment with faricimab 8-weekly and faricimab PTI was associated with a numerically higher incidence and total number of serious adverse events compared to aflibercept 8-weekly in the YOSEMITE trial, this pattern was not observed in the RHINE trial.

6.33 The Pre-PBAC Response claimed that, with the exception of cataract, intraocular pressure increases, and vitreous floaters, the incidence of ocular adverse events occurring in the study eye was comparable across treatment arms. The Pre-PBAC Response also claimed that almost all of the ocular adverse events were mild to moderate in severity, and ocular adverse events suspected to be related to study treatment were low. In addition, the incidence of serious ocular adverse events at the final analysis remained low but noted that serious ocular adverse events were slightly

higher in the faricimab PTI arm compared to the faricimab 8-weekly and aflibercept arms. The Pre-PBAC Response reiterated the claim that treatment with faricimab is associated with comparable safety outcomes compared to aflibercept.

6.34 The submission presented additional safety data for faricimab from the BOULEVARD trial (DMO) and the TENAYA and LUCERNE trials (neovascular AMD). While the incidence of adverse events in the BOULEVARD trial appeared broadly similar between treatment arms, there was a relatively small number of patients in each arm of the trial, and the dose of ranibizumab used in the trial (0.3 mg) was lower than the dose of ranibizumab used in Australian clinical practice (0.5 mg).

6.35 The incidence of treatment-emergent adverse events and total number of adverse events were similar between the faricimab and aflibercept treatment arms in the TENAYA/LUCERNE trials. The incidence of serious adverse events and the total number of serious adverse events were numerically higher in the aflibercept 2 mg arm compared to the faricimab 6 mg treatment arm.

Benefits/harms

6.36 Given the claim of non-inferiority for faricimab versus aflibercept, a comparison of benefits and harms is not presented.

Clinical claim

6.37 The submission described faricimab (6 mg administered 8-weekly or based on a PTI) as non-inferior to aflibercept (2 mg administered 8-weekly) in terms of effectiveness and safety in patients with visual impairment due to DMO.

6.38 The submission also claimed that while maintaining similar efficacy outcomes, extended treatment intervals (up to 16 weeks) for faricimab provide a meaningful reduction in the frequency of treatment administration and therefore potentially reduced treatment burden in patients with DMO. The evaluation noted that while treatment with faricimab PTI was associated with similar efficacy outcomes compared to faricimab 8-weekly, it is unclear whether listing of faricimab will result in reduced treatment burden for patients, as the administration frequency for VEGF inhibitors in clinical practice may be similar to faricimab PTI if used as part of a treat-and-extend regimen. There is a lack of available clinical evidence comparing faricimab PTI to treat-and-extend regimens for aflibercept or ranibizumab.

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

6.40 In terms of comparative safety, the PBAC noted the incidence of treatment-emergent and serious adverse events was numerically higher in the faricimab 8-weekly arm compared to the aflibercept 8-weekly arm, suggesting that the safety of faricimab may be worse than aflibercept. While the incidence of adverse events in the faricimab PTI and aflibercept 8-weekly 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

6.41 The submission stated that a cost-minimisation approach 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 drug and administration costs were not included in the proposed price of faricimab.

6.42 The cost analysis presented in the submission was based on the published price of aflibercept.

6.43 The submission noted that aflibercept was previously recommended for listing for the treatment of DMO on a cost-minimisation basis with ranibizumab. The equi-effective doses are aflibercept 2 mg injection and 0.5 mg ranibizumab injection.

6.44 There are differences between aflibercept and ranibizumab in the recommended administration frequencies, particularly in the first year of treatment. The aflibercept product information states that, when used for the treatment of DMO, treatment should be initiated with one injection per month for five consecutive months, followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. The ranibizumab product information states that treatment should be initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. The DUSC previously noted that the number of injections per patient in the first 12 months of treatment was similar for aflibercept and ranibizumab (p32, 'Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO', May 2018, DUSC public release document).

6.45 The equi-effective doses (steady state) proposed in the submission were: 5.20 doses of faricimab annually are equi-effective to 7.86 doses of aflibercept 2 mg annually.

6.46 The cost analysis was conducted over a two-year time horizon to account for differences in costs in the first and subsequent years.

6.47 The number of administrations assumed in the initial year of treatment for faricimab (8.23 administrations) was based on the mean number of doses over the first year of the RHINE and YOSEMITE trials. The number of administrations in the second year of treatment was derived from the distribution of use among patients in the faricimab

PTI arm at Week 52 in the RHINE and YOSEMITE trials (5.20 administrations; see table below).

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

Interval	Doses	Proportion of patients on each dose interval	
		RHINE (N=308)	YOSMITE (N=286)
4-weekly	13.0	13%	11%
8-weekly	6.5	16%	15%
12-weekly	4.3	22%	21%
16-weekly	3.3	51%	53%
Trial based average number of doses		5.36	5.03
Participant weighted trial-based average number of yearly doses		5.20[1]	

Source: Table 3.2, p102 of the submission.

[1] Correction of an error in the cost-minimisation spreadsheet (cell E75 changed from 68/308 to 62/308) resulted in an estimated 5.16 administrations per year.

6.48 The number of administrations assumed in the initial and subsequent year of treatment with aflibercept (8.71 and 7.86 administrations, respectively) were based on the weighted utilisation for aflibercept and ranibizumab reported in the 2018 DUSC analysis ('Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO', May 2018, DUSC public release document).

6.49 An update to the analysis in the 2018 DUSC report, based on patients who received intravitreal aflibercept and ranibizumab under DMO authority codes and initiated treatment in 2018 from PBS data, was conducted during the evaluation. The mean and median number of aflibercept/ranibizumab administrations in the first and second years of treatment (counted from initiation date) are summarised in the table below.

Table 10: Intravitreal VEGF inhibitor PBS scripts per year: patients initiating treatment in 2015/16 versus 2018

	Patients initiating treatment in 2015/16		Patients initiating treatment in 2018	
	No. patients	Scripts per year (mean)	No. patients	Scripts per year (mean)
Year 1	2015: 3,390 2016: 4,756	2015: 9.79 2016: 8.71	3,994	6.38
Year 2	2,938[1]	7.86[1]	2,348	5.27

Source: Table 17, p31; Table 18, p32; Table 19, p32 of the 2018 DUSC analysis; Updated analysis provided by the DUSC Secretariat.

[1] Patients who initiated treatment in 2015 and continued treatment for a second year.

6.50 The updated PBS data suggests that the average number of scripts per patient in the first year of treatment decreased from 8.71 (patients initiating treatment in 2016) to 6.38 (patients initiating treatment in 2018). The average number of scripts per patient in their second year of treatment also decreased from 7.86 (patients initiating treatment in 2015) to 5.27 (patients initiating treatment in 2018). This is likely due predominantly to the increasing use of treat-and-extend regimens for DMO in Australian clinical practice.

6.51 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 average

number of scripts per patient from PBS data 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	8.23	8.71	8.23	6.38
Drug cost (DPMQ/AEMP × administration frequency)	$8,584	$9,084	$7,675	$5,949
Administration cost ($312.95[1] × administration frequency)	$2,576	$2,726	$2,576	$1,997
Total cost Year 1	$11,160	$11,810	$10,250	$7,945
Incremental cost Year 1	-$650		$2,305	
Year 2				
Administration frequency	5.20	7.86	5.20	5.27
Drug cost (DPMQ/AEMP × administration frequency)	$5,425	$8,198	$4,850	$4,914
Administration cost ($312.95[1] × administration frequency)	$1,628	$2,460	$1,628	$1,649
Total cost Year 2	$7,053	$10,657	$6,478	$6,563
Incremental cost Year 2	-$3,605		-$85	
Total cost over 2 years	**$18,213**	**$22,467**	**$16,728**	**$14,508**
Incremental cost over 2 years	**-$4,254**		**$2,220**	

Source: Cost minimisation analysis spreadsheet; Table 3.6, p105 of the submission.
Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity
[1] Administration costs based on MBS items 42738, 42739, 42740: intravitreal injection of therapeutic substances

6.52 The submission estimated a net saving of $4,254 for faricimab compared to aflibercept over a two-year time horizon ($18,213 versus $22,467). It is likely that the net cost savings attributed to faricimab have been overestimated, as the analysis is highly dependent on the frequency of use of intravitreal anti-VEGF medicines 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 compared to the 2018 data.
- The number of doses of faricimab was based on clinical trial conditions and may overestimate the number of doses compared to clinical practice.
- 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.

6.53 The Pre-PBAC Response presented the results of an updated cost analysis for faricimab versus aflibercept, with a faricimab administration frequency of 4.68 administrations per year in subsequent years (previously 5.20 administrations per year), based on an

analysis of faricimab administration frequency at Week 96 in the RHINE/YOSEMITE trials. The administration frequency for aflibercept was based on the revised DUSC estimate for aflibercept (5.27 administrations per year). The table below presents the results of the Pre-PBAC Response cost analysis, along with an alternative approach conducted at the AEMP level.

Table 12: Results of updated cost analysis (Year 2)

	Sponsor's approach		Alternative approach	
	Faricimab	Aflibercept	Faricimab	Aflibercept
	DPMQ $1,042.95		AEMP $932.40	
Administration frequency	4.68	5.27	4.68	5.27
Drug cost (DPMQ/AEMP × administration frequency)	$4,882	$5,496	$4,364	$4,914
Administration cost ($312.95[1] × administration frequency)	$1,465	$1,649	$1,465	$1,649
Total cost Year 2	$6,347	$7,146	$5,829	$6,563
Incremental cost Year 2	**-$799**		**-$734**	

Source: Cost minimisation analysis spreadsheet provided with pre-PBAC response.
Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity
[1] Administration costs based on MBS items 42738, 42739, 42740: intravitreal injection of therapeutic substances.

6.54 The submission presented the results of sensitivity analyses based on alternative time horizons (5 and 10 years), dose relativities (25% higher administrations, 50% higher administrations, no difference in administrations), trial-based administrations, and based on a patient perspective. The submission noted that the results were cost-saving in all scenarios, apart from the scenario assuming no difference in faricimab and aflibercept administration frequency, which was cost neutral.

Drug cost/patient/year

6.55 The drug cost per patient for faricimab is $8,583 in the initial year of treatment (based on the proposed published DPMQ of $1,042.95 x 8.23 administrations), and $5,423 in each subsequent year (based on the proposed published DPMQ of $1,042.95 x 5.20 administrations). Based on the updated cost analysis for faricimab versus aflibercept in the Pre-PBAC Response, the drug cost per patient for faricimab is $4,881.01 in each subsequent year (based on the proposed published DPMQ of $1,042.95 x 4.68 administrations).

6.56 The drug cost per patient for aflibercept is $9,084 in the initial year of treatment (based on the published DPMQ of $1,042.95 x 8.71 administrations), and $8,198 in each subsequent year (based on the published DPMQ of $1,042.95 x 7.86 administrations). Based on the updated DUSC Secretariat analysis, the drug cost per patient for aflibercept is $6,654 in the initial year of treatment (based on the published DPMQ of $1,042.95 × 6.38 administrations) and $5,496 in each subsequent year (based on the published DPMQ of $1,042.95 × 5.27 administrations).

Estimated PBS usage & financial implications

6.57 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial implications of listing faricimab on the PBS for the treatment of DMO. The financial estimates were based on the published prices of faricimab, aflibercept and ranibizumab.

6.58 Key inputs used to derive the financial estimates are presented in the table below.

Table 13: Data sources and parameter values used in the estimated utilisation and financial implications

Data	Value	Source	Comment
Eligible population			
Number of eligible scripts	2020: 82,504	PBS data for calendar year 2020 for ranibizumab (PBS items 10373Y, 10374B), and aflibercept (PBS items 10505X, 12153P), the only other VEGF medicines currently listed on the PBS for the treatment of DMO.	This was reasonable.
Estimated annual rate of growth of eligible scripts	Year 1: 9.88% Year 2: 10.17% Year 3: 8.73% Year 4: 7.53% Year 5: 7.58% Year 6: 6.95%	Estimated by linear extrapolation of total PBS and RPBS items for ranibizumab and aflibercept from 2016 to 2020.	The submission assumed that PBS listing of faricimab will not increase the eligible market size. This assumption was considered uncertain.
Uptake of faricimab	Year 1: 45% Year 2: 50% Year 3: 55% Year 4: 60% Year 5: 60% Year 6: 60%	Assumption based on the sponsor's internal estimates.	Estimated uptake of faricimab is highly uncertain and likely overestimated. While faricimab has the theoretical advantage of targeting two pathways involved in the pathogenesis of DMO, the clinical trials suggest that faricimab has similar effectiveness compared to anti-VEGF treatment (aflibercept).
Treatment utilisation			
Average number of scripts per person per year (ranibizumab and aflibercept)	7.86 scripts/year	DUSC 2018 report into the utilisation of ranibizumab and aflibercept (Table 18, p32) - mean number of VEGF inhibitor injections supplied in Year 2 of therapy for patients initiating PBS subsidised 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.
Average number of faricimab scripts per person per year	5.20 scripts/year	Based on the weighted mean administration frequency in the RHINE/YOSEMITE trials at Week 52.	Trial based utilisation data impacted by pre-specified dosing protocols may not reflect use in the Australian setting.
Script substitution rate	1.0 ranibizumab or aflibercept script = 0.66 faricimab scripts	Based on the equi-effective doses proposed in the submission for Year 2 onward. Calculated as 5.20 faricimab administrations / 7.86 aflibercept/ranibizumab administrations.	Equi-effective doses were based on scripts in the second and subsequent years of therapy and do not account for loading doses in the first year of treatment.
Costs			

Data	Value	Source	Comment
Faricimab (intravitreal)	DPMQ: $1,042.95 (proposed)	Proposed price (published) based on the published AEMP of ranibizumab and aflibercept ($932.40).	-
Ranibizumab and aflibercept (intravitreal)	DPMQ: $1,042.95 (published)	Ranibizumab: Items 1382R, 10138N Aflibercept: Items 2168D, 12152N (published AEMP of $932.40).	-
Weighted patient copayment PBS/RPBS	PBS: $20.58 (98.61%) RPBS: $6.28 (1.39%)	Ranibizumab and aflibercept PBS utilisation data for 2020 calendar year weighted by beneficiary type.	This was reasonable.
Administration of intravitreal aflibercept and ranibizumab	Fee: $312.95 Benefit 80%: $250.36	MBS items 42738, 42739, 42740 (paracentesis of anterior chamber or vitreous cavity or both; intravitreal injection of therapeutic substances).	This was reasonable.

Source: Table 4.2, p.102; Table 4.3, p.103-104 of the submission; Section 4 workbook
Abbreviations: DMO = diabetic macular oedema; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; MBS = medical benefits schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; VEGF = vascular endothelial growth factor

6.59 The estimated utilisation and financial impact of listing faricimab for DMO presented in the submission are summarised in the table below.

Table 14: Estimated use and financial implications of listing faricimab for DMO

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Estimated ranibizumab scripts	[1]	[1]	[2]	[2]	[2]	[2]
Estimated aflibercept scripts	[3]	[4]	[4]	[5]	[6]	[6]
Estimated total scripts	[6]	[6]	[6]	[6]	[6]	[6]
Faricimab uptake rate	45%	50%	55%	60%	60%	60%
Estimated substituted scripts	[7]	[8]	[9]	[3]	[4]	[4]
Faricimab scripts (substituted scripts x 0.66)	[1]	[2]	[7]	[8]	[8]	[8]
Cost to PBS/RPBS	$[10]	$[10]	$[11]	$[12]	$[12]	$[13]
Less patient co-payments	-$[14]	-$[14]	-$[14]	-$[14]	-$[14]	-$[14]
Total net cost to PBS/RPBS	**$[10]**	**$[10]**	**$[11]**	**$[12]**	**$[12]**	**$[13]**
Offset ranibizumab scripts	-[15]	-[15]	-[15]	-[1]	-[1]	-[1]
Offset aflibercept scripts	-[2]	-[7]	-[7]	-[8]	-[9]	-[9]
Total offset scripts	-[7]	-[8]	-[9]	-[3]	-[4]	-[4]
Offsets to PBS/RPBS	-$[11]	-$[12]	-$[13]	-$[16]	-$[16]	-$[17]
Less patient co-payments	-$[14]	-$[14]	-$[14]	-$[14]	-$[14]	-$[14]
Net offsets to PBS/RPBS	-$[11]	-$[12]	-$[13]	-$[18]	-$[16]	-$[17]
Net cost to PBS/RPBS	**-$[19]**	**-$[19]**	**-$[20]**	**-$[20]**	**-$[20]**	**-$[10]**
MBS costs faricimab	$[20]	$[20]	$[10]	$[10]	$[11]	$[11]
MBS cost offsets ranibizumab/aflibercept	-$[10]	-$[11]	-$[11]	-$[12]	-$[13]	-$[13]
Net cost to MBS	-$[19]	-$[19]	-$[19]	-$[19]	-$[20]	-$[20]
Overall Net cost to Gov't	**-$[20]**	**-$[10]**	**-$[10]**	**-$[11]**	**-$[12]**	**-$[12]**

Source: Tables 4.4 and 4.5, p122; Table 4.6, p123; Table 4.13, p126; Table 4.14, p128 of the submission; Section 4 workbook
Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
The redacted values correspond to the following ranges:
[1] 20,000 to < 30,000
[2] 30,000 to < 40,000
[3] 70,000 to < 80,000
[4] 80,000 to < 90,000

[5]90,000 to < 100,000
[6]100,000 to < 200,000
[7]40,000 to < 50,000
[8]50,000 to < 60,000
[9]60,000 to < 70,000
[10]$30 million to < $40 million
[11]$40 million to < $50 million
[12]$50 million to < $60 million
[13]$60 million to < $70 million
[14]$0 to < $10 million
[15]10,000 to < 20,000
[16]$80 million to < $90 million
[17]$90 million to < $100 million
[18]$70 million to < $80 million
[19]$10 million to < $20 million
[20]$20 million to < $30 million

6.60 Based on the published prices of aflibercept and ranibizumab, the net cost savings of listing faricimab for DMO on PBS/RPBS was estimated to be $10 million to < $20 million in Year 1, increasing to savings of $30 million to < $40 million in Year 6, with a cumulative saving of $100 million to < $200 million over the first 6 years of listing. Including additional savings from the proposed reduced MBS administration costs, the net cost savings to Government were estimated to be $20 million to < $30 million in Year 1, increasing to $50 million to < $60 million Year 6, with cumulative savings of $200 million to < $300 million over the first 6 years of listing.

6.61 The evaluation noted the estimated cost savings are dependent on the assumed dose frequencies and may not be realised if the dose frequencies differ in clinical practice. Adjusted estimates derived during the evaluation based on the updated DUSC Secretariat analysis (5.27 scripts per patient for aflibercept and ranibizumab) are summarised below. The adjustment resulted in lower estimated cost savings to PBS/RPBS of $0 to < $10 million in Year 1, increasing to savings of $0 to < $10 million in Year 6, a cumulative savings of $0 to < $10 million over the first 6 years of listing. Incorporation of reduced costs to MBS resulted in an overall net cost savings to Government of $0 to < $10 million over 6 years.

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

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Estimated ranibizumab scripts	[1]	[1]	[2]	[2]	[2]	[2]
Estimated aflibercept scripts	[3]	[4]	[4]	[5]	[6]	[6]
Estimated total scripts	[6]	[6]	[6]	[6]	[6]	[6]
Faricimab uptake rate	45%	50%	55%	60%	60%	60%
Estimated substituted scripts	[7]	[8]	[9]	[3]	[4]	[4]
Faricimab scripts (substituted scripts x 0.99)	[7]	[8]	[9]	[3]	[4]	[4]
Cost to PBS/RPBS	$[10]	$[11]	$[12]	$[13]	$[14]	$[15]
Less patient co-payments	-$[16]	-$[16]	-$[16]	-$[16]	-$[16]	-$[16]
Total net cost to PBS/RPBS	**$[10]**	**$[11]**	**$[12]**	**$[13]**	**$[14]**	**$[15]**

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Offset ranibizumab scripts	[17]	[17]	[17]	[1]	[1]	[1]
Offset aflibercept scripts	[2]	[7]	[7]	[8]	[9]	[9]
Total offset scripts	[7]	[8]	[9]	[3]	[4]	[4]
Offsets to PBS/RPBS	-$[10]	-$[11]	-$[12]	-$[14]	-$[14]	-$[15]
Less patient co-payments	-$[16]	-$[16]	-$[16]	-$[16]	-$[16]	-$[16]
Net offsets to PBS/RPBS	**-$[10]**	**-$[11]**	**-$[12]**	**-$[13]**	**-$[14]**	**-$[15]**
Net cost to PBS/RPBS	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**
MBS costs faricimab	$[18]	$[10]	$[10]	$[11]	$[12]	$[12]
MBS cost offsets ranibizumab/aflibercept	-$[18]	-$[10]	-$[10]	-$[11]	-$[12]	-$[12]
Net cost to MBS	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**
Overall Net cost to Gov't	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**	**-$[16]**

Source: Calculated during the evaluation using updated DUSC Secretariat estimates of average scripts/year for aflibercept and ranibizumab.
Abbreviations: DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee.
The redacted values correspond to the following ranges:
[1]20,000 to < 30,000
[2]30,000 to < 40,000
[3]70,000 to < 80,000
[4]80,000 to < 90,000
[5]90,000 to < 100,000
[6]100,000 to < 200,000
[7]40,000 to < 50,000
[8]50,000 to < 60,000
[9]60,000 to < 70,000
[10]$40 million to < $50 million
[11]$50 million to < $60 million
[12]$60 million to < $70 million
[13]$70 million to < $80 million
[14]$80 million to < $90 million
[15]$90 million to < $100 million
[16]$0 to < $10 million
[17]10,000 to < 20,000
[18]$30 million to < $40 million

6.62 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 DMO, 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 additional dose requirements in the initial year of treatment with faricimab which would further reduce the assumed cost savings to Government.

6.63 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

6.64 No quality use of medicines issues were raised in the submission, and no activities to support the quality use of medicines were proposed.

Financial Management – Risk Sharing Arrangements

6.65 No risk-sharing arrangements were proposed.

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 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 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: 8.23 doses of faricimab annually to 6.38 doses of aflibercept 2 mg annually
- Year 2: 4.68 doses of faricimab annually to 5.27 doses of aflibercept 2 mg annually.

The PBAC accepted the faricimab administration frequency based on an analysis of faricimab administration frequency in the RHINE/YOSEMITE trials and the aflibercept administration frequency was based on PBS data.

7.3 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 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 RHINE/YOSEMITE 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 RHINE of YOSEMITE 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, brolucizumab PSD, November 2019), was met.

7.6 The PBAC noted that there were numerically higher adverse events, including serious adverse events and adverse events of special interest, following treatment with faricimab compared to aflibercept in both the RHINE and YOSEMITE trials. The PBAC noted that the increased adverse events associated with treatment with faricimab were mostly minor events (conjunctival haemorrhage, eye irritation, eye pruritis, ocular hyperaemia). The PBAC also noted that adverse events for VEGF inhibitors in clinical practice are likely to be dependent 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.

7.7 The Pre-PBAC Response provided final clinical study reports for the RHINE and YOSEMITE trials, which report outcomes based on a mean treatment duration of 90 weeks in the RHINE trial and 88 weeks in the YOSEMITE trial (the submission was based on the results of the primary analysis for the RHINE and YOSEMITE trials, corresponding to a mean treatment duration of 54 weeks in the RHINE trial and 53 weeks in the YOSEMITE trial). Due to the scope of the final clinical study report documents, the full results for the RHINE and YOSEMITE trials 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 RHINE and YOSEMITE trials provided in the original submission.

7.8 The PBAC accepted the market share approach to estimate the financial impact of listing faricimab on the PBS for DMO. 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. The PBAC noted that, even if the products are cost minimised to each other

and if there is no growth in the market as a result, patients shifting from another VEGF inhibitor to faricimab could have a financial impact. The PBAC also noted that this cost may be partially offset by savings in subsequent years but still considered that the total financial impacts had some persistent uncertainty.

7.9 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 an analysis of faricimab administration frequency in the RHINE/YOSEMITE trials and the aflibercept administration frequency was based on the PBS data for aflibercept.

7.10 The PBAC noted the requested listing and considered that 5 repeats would be appropriate for faricimab for all treatment phases. The PBAC noted that this was consistent with aflibercept and ranibizumab, which are also 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, 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).

7.13 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.

7.14 The PBAC advised that faricimab is not suitable for prescribing by nurse practitioners.

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

7.16 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.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	5	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	5	Vabysmo

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒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: 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
	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: Authority approval for initial treatment of each eye must be sought. 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 Diabetic Macular Oedema (DMO) - 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**	**№.of Rpts**	**Available brands**
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	5	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	5	Vabysmo

		Category / Program: GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical
		Restriction type: ☒Authority Required – (STREAMLINED)
		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: 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
		AND
		Clinical criteria:
		Patient must have previously been issued with an authority prescription for this drug 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

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FARICIMAB					
faricimab 28.8 mg / 0.24 mL solution for injection, vial	NEW	1	1	5	Vabysmo
faricimab 24.0 mg / 0.2 mL solution for injection, pre-filled syringe	NEW	1	1	5	Vabysmo

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical
	Restriction type: ☒Authority Required – Written
	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
	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:
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	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 Diabetic Macular Oedema (DMO) - 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 diabetic macular oedema.

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