5.03 BROLUCIZUMAB, Solution for intravitreal injection 19.8 mg in 0.165 mL pre-filled syringe, Beovu®, Novartis Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 85, Authority Required listing for brolucizumab for treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD). Brolucizumab has not previously been considered by the PBAC.

1.2 The requested listing was based on a cost-minimisation analysis of brolucizumab to aflibercept in the proposed target population. The key components of the clinical issue addressed by the submission are summarised below (Table 1).

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

Component	Description
Population	Patients with neovascular (wet) AMD
Intervention	Brolucizumab
Comparator	Aflibercept and ranibizumab[a]
Outcomes	Improvement in BCVA in the affected eye Proportion of eyes with ≥15 letter gains in BCVA or BCVA of ≥84 letters in the affected eye Proportion of eyes with ≥15 letter loss in BCVA in the affected eye Reduction of disease activity Quality of life (Visual Function Questionnaire-25) Change from baseline in Central Subfield Thickness Percent of patients who need 8-weekly injections Adverse events
Clinical claim	Brolucizumab is non-inferior in terms of efficacy and equivalent in terms of safety compared to the VEGF inhibitors aflibercept and ranibizumab when used in the treatment of wet AMD.

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; VEGF = vascular endothelial growth factor.
[a] Aflibercept was proposed as the main comparator, and ranibizumab was considered a secondary comparator
Source: Table 1.1, Section 1 of the submission.

2 Requested listing

2.1 The proposed listing is summarised below. Suggested additions are in italics and suggested deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BROLUCIZUMAB 19.8 mg in 0.165 mL syringe	1	2	Effective: $[redacted] Published: $[redacted]	Beovu	Novartis Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Subfoveal choroidal neovascularisation
PBS Indication:	Subfoveal choroidal neovascularisation
Treatment phase:	Initial *treatment*
Restriction Level:	☒Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	The condition must be due to age-related macular degeneration (AMD), AND The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fluorescein angiography, AND The treatment must be the sole PBS-subsidised therapy for this condition.
~~**Population criteria:**~~	~~N/A~~
Prescriber Instructions	Authority approval for initial treatment of each eye must be sought. The first authority application for each eye must be made in writing or by telephone. 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. A telephone application must be made following submission by facsimile of a copy of a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form and a copy of the optical coherence tomography or fluorescein angiogram report.
Administrative Advice	The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 No increase in the maximum number of repeats may be authorised. *No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.* *Where both eyes are being treated simultaneously, a quantity of 2 vials can be requested on the same authority prescription form.* Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BROLUCIZUMAB 19.8 mg in 0.165 mL syringe	1	2	Effective: $[redacted] Published: $[redacted]	Beovu Novartis Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Subfoveal choroidal neovascularisation
PBS Indication:	Subfoveal choroidal neovascularisation
Treatment phase:	Continuing *treatment*
Restriction level:	☒Authority Required – Telephone/ *Electronic*
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.
Clinical criteria:	Patient must have previously been granted an authority prescription for the same eye. AND The condition must be due to age-related macular degeneration (AMD), AND The treatment must be the sole PBS-subsidised therapy for this condition,
Administrative Advice	*Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services.* *Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* No increase in the maximum number of repeats may be authorised. *No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.* *Where both eyes are being treated simultaneously, a quantity of 2 vials can be requested on the same authority prescription form.* Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BROLUCIZUMAB 19.8 mg in 0.165 mL syringe	1	2	Effective: $[redacted] Published: $[redacted]	Beovu Novartis Australia Pty Ltd

Episodicity:	Chronic
Condition:	~~Age-related macular degeneration~~ *Subfoveal choroidal neovascularisation*
PBS Indication:	Subfoveal choroidal neovascularisation ~~(CNV)~~
Treatment phase:	~~Grandfather clause~~ *Grandfathered treatment*
Restriction Level:	☒Authority Required - In Writing ☒Authority Required - Telephone
Treatment criteria:	Must be treated by an ophthalmologist or in consultation with an ophthalmologist.

Clinical criteria:	The condition must be due to age-related macular degeneration (AMD), AND Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date], AND Patient must have documented history that the condition has been diagnosed by optical coherence tomography; OR fluorescein angiography, *AND* *The treatment must be the sole PBS-subsidised therapy for this condition.*
Population criteria:	N/A

2.2 The submission requested a special pricing arrangement (SPA) for brolucizumab, on a cost-minimisation basis with the effective prices of aflibercept and ranibizumab, which are both currently subject to SPAs. The submission proposed an effective price of $[redacted], on the basis of Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth (the Strategic Agreement) that, until expiration of the agreement 30 June 2022, brolucizumab can be listed with a price equivalent to that of the other anti-vascular endothelial growth factor (anti-VEGF) drugs prior to the application of any F1 statutory cuts.

2.3 The population in the requested listing was narrower than that in the proposed TGA indication and the trial populations. The proposed listing restricted eligibility to patients with subfoveal CNV, while the proposed TGA indication was for the treatment of neovascular AMD, irrespective of the location of the CNV. While the majority of the patients in two of the three brolucizumab trials presented in the submission had subfoveal CNV lesions (84% in the HAWK trial, and 100% in OSPREY), only 32% of participants in the HARRIER trial had subfoveal lesions. The Pre-Sub-Committee Response (PSCR) stated that while it is acknowledged that patients with subfoveal lesions in the HARRIER trial comprised a relatively smaller proportion, the extent of visual impairment in terms of best corrected visual acuity (BCVA) letters read in the HAWK and HARRIER trials were similar at baseline, with similar improvements in BCVA in the brolucizumab treatment arms, a similar proportion of patients achieving a ≥15 letter gain in BCVA or BCVA >84, and a similar proportion of patients achieving ≥73 letters, suggesting that lesion location does not result in significant treatment effect modification.

2.4 The proposed listing for brolucizumab was consistent with the current PBS listings for aflibercept and ranibizumab for the treatment of subfoveal CNV due to AMD.

2.5 Under the proposed restriction, patients who are intolerant or contraindicated to, or who have inadequate response to other anti-VEGF treatments, would be able to switch to brolucizumab. All of the trials presented in the submission excluded patients who had received prior treatment for neovascular AMD in the study eye. The PSCR stated (p3) that findings from three systematic reviews of 95 studies confirm that switching anti-VEGF therapy can offer improved anatomical benefits, and although this evidence is not specific to brolucizumab, the similar mechanism of action would

suggest it would be appropriate to switch patients between anti-VEGFs. However, the Economics Sub-Committee (ESC) advised that brolucizumab is a smaller molecule that has different pharmacodynamic properties and safety profiles to currently PBS listed anti-VEGFs.

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process and was not TGA registered at the time of PBAC consideration. The second round Clinical Evaluation Report and TGA Delegate's Overview were provided prior to the PBAC meeting. The Delegate's Overview stated [redacted] However, the Delegate noted the [redacted]

4 Population and disease

4.1 AMD 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. There are two types of AMD: the non-neovascular (atrophic) or dry form, and the neovascular (exudative) or wet form.

4.2 Neovascular (wet) AMD is characterised by CNV, a process in which new blood vessels grow beneath the retina and macula. These blood vessels leak, causing separation of Bruch's membrane, the retinal pigment epithelium (RPE) and the retina from each other, with accumulation of sub-RPE, sub-retinal or intra-retinal fluid. VEGF is widely considered the main growth factor responsible for this neovascularisation.

4.3 CNV lesions are classified according to the location of the lesion relative to the fovea: subfoveal (located directly below the fovea), extrafoveal (located adjacent to fovea) and juxtafoveal (located away from the fovea).

4.4 The submission requested listing of brolucizumab, an anti-VEGF agent, as an alternative treatment option to the anti-VEGF agents currently listed on the PBS for the treatment of subfoveal CNV due to AMD (aflibercept and ranibizumab).

4.5 The PBAC noted that there was no difference in the intended patient population for brolucizumab compared with populations for other PBS-listed anti-VEGF agents (aflibercept and ranibizumab).

5 Comparator

5.1 The submission nominated aflibercept as the main comparator and ranibizumab as a secondary comparator. While aflibercept is the market leader, ranibizumab has become the least costly comparator since the F1 anniversary price cuts applied to

ranibizumab (10%) and aflibercept (5%) on 1 April 2018. Aflibercept and ranibizumab have been previously considered by the PBAC as non-inferior to each other for the treatment of neovascular AMD.

5.2 The submission requested that the pre-statutory cut comparator price applies to brolucizumab, according to Clause 5.7 of the Strategic Agreement. The PSCR stated (p4) that if the Minister (or Delegate) determines that Clause 5.7 applies, then ranibizumab and aflibercept have the same price [in terms of a cost minimisation price for brolucizumab]. The PBAC noted that application of the Strategic Agreement is not a matter for PBAC.

5.3 If treatment with brolucizumab is substantially more costly than any of the alternative therapies (aflibercept and ranibizumab), the PBAC could only recommend listing brolucizumab if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies (National Health Act 1953, Section 101(3B)). The PBAC considered that brolucizumab did not satisfy these requirements, and advised that the cost minimisation should be performed against the least costly comparator, ranibizumab, so that it is not more costly than any of the alternative therapies.

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 the Macular Disease Foundation Australia via the Consumer Comments facility on the PBS website. The comments mainly described the benefit of having an additional treatment option for patient with AMD and they welcomed the increased interval between injections observed in the clinical trials (HAWK and Harrier). They also outlined the burdens of intravitreal injections in particular, the cost of treatment, discomfort, emotional trauma and inconvenience for both the patients and their carers, and that this challenge is magnified for elderly people and for people living in rural or remote locations. They also indicated that one of the advantages of less frequent dosing offered by brolucizumab should translate to a lowered risk of injection-related ocular complications such as endophthalmitis.

Clinical trials

6.3 The submission was based on two head-to-head randomised trials comparing brolucizumab 6 mg to aflibercept 2 mg (HAWK (n=720) and HARRIER (n=739))*, and one supplementary randomised trial comparing brolucizumab 6 mg and aflibercept 2 mg (OSPREY, n=89), in patients with neovascular AMD.

6.4 Details of the trials presented in the submission are provided in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HAWK	Clinical Study Report: Two year randomised double masked multicentre three arm study comparing the efficacy and safety of RTH258 versus aflibercept in subjects with neovascular age related macular degeneration.	December 2018
	Clinical Study Report: A 24-week, double-masked, multicenter, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in subjects with neovascular age-related macular degeneration who have completed the CRTH258A2301 study.	December 2018
HARRIER	Clinical Study Report: A two year randomised double masked multicentre two arm study comparing the efficacy and safety of RTH258 6 mg versus aflibercept in subjects with neovascular age related macular.	December 2018
HAWK and HARRIER	Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration.	*Ophthalmology* 2019 Apr 12 (Epub ahead of print).
OSPREY	Clinical Study Report: A prospective, randomised, double-masked, multicentre, two arm study comparing the efficacy and safety of ESBA1008 versus Eylea in subjects with exudative age related macular degeneration	November 2015
	Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age related macular degeneration; a randomised trial.	*Ophthalmology* 2017; 124(9): 1296-1304.

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

6.5 The key features of the direct randomised trials are summarised in Table 3 below.

Table 3: Key features of the included evidence

Trial	N[a]	Design/duration	Risk of bias	Patient population	Outcomes
brolucizumab vs. aflibercept					
HAWK	720[b]	R, DB 96 weeks	Unclear	Patients with CNV due to AMD	Change in BCVA from baseline to Week 48 or Week 96
HARRIER	739	R, DB 96 weeks	Low	As above	As above
Meta-analysis	1459	Included HAWK and HARRIER			As above
OSPREY	89	R, DB 56 weeks	Low	As above	Change in BCVA from baseline to Week 12 or Week 40

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularisation; DB = double blind; R = randomised.

[a] Number of patients in the full analysis set (FAS).

[b] This is the number of patients in the 6 mg brolucizumab and 2 mg aflibercept arms. HAWK was a three-armed trial comparing two doses

* Number of patients in the relevant treat arms (full analysis set)

of brolucizumab (3 mg and 6 mg) with aflibercept 2 mg. The total number of patients in all three arms was 1078 (FAS).
Source: Sections 2.3 to 2.4 of the submission.

6.6 In all three trials, missing data were imputed using last observation carried forward. The extent of missing/censored data at each assessment visit could not be located in the Clinical Study Reports (CSRs). While loss to follow-up was low in all three trials, in HAWK, the proportion of patients discontinuing treatment was relatively high, with 18.8% in the brolucizumab 6 mg arm and 22.2% in the aflibercept 2 mg arm discontinuing prior to Week 96. The main reasons for early treatment discontinuation were withdrawal by subject and AEs. While supportive analyses that used a mixed model repeated measures with observed data were consistent with the primary analyses, the potential for bias from this source was unclear.

6.7 In HAWK and HARRIER, patients in both the brolucizumab and the aflibercept treatment arms received 3 loading doses administered at monthly intervals (Day 0, Week 4 and Week 8), followed by maintenance regimens:

- Brolucizumab 6 mg every 12 or 8 weeks (q12/8w), depending on whether there was evidence of disease activity;
- Aflibercept 2 mg every 8 weeks (q8w).

6.8 The submission claimed that the brolucizumab treatment regimen used in HAWK and HARRIER was consistent with the recommendations in the draft brolucizumab PI. The draft PI stated that after the initial three monthly loading doses, brolucizumab should be administered every 12 weeks, but that the physician may individualise treatment intervals based on disease activity, and that the dosing interval could be as frequent as every 8 weeks. The PSCR argued that the absence of disease activity during the initial q12w cycle was a strong predictor for remaining on the q12w treatment interval and the objective of the initial q12w dosing interval was to identify subjects that required more frequent dosing interval. Subjects identified with a q8w need were switched to a q8w treatment interval for the remainder of the study. However, the PBAC noted that patients receiving brolucizumab in the HAWK and HARRIER trials could only have a dose modification from q12w dosing to q8w dosing, which was inconsistent with the individualised treatment described in the draft PI. This lack of flexibility in the dosing regimen applied in the trial may have resulted in some patients being treated more frequently than required to control disease activity.

6.9 Aflibercept was administered every 8 weeks following the initial 3 loading doses administered at monthly intervals. This was not consistent with the treatment strategy most commonly employed in Australian clinical practice and described in the aflibercept PI, where the treatment interval is extended by increasing intervals in 2- or 4-weekly increments while maintaining stable visual and/or anatomic outcomes (treat and extend [T&E] regimen), and may also be shortened to a minimum of 4 weeks, if there is evidence of disease activity. The PSCR acknowledged this inconsistency; however, the Sponsor argued that evidence from several meta-

analyses and systematic reviews found that outcomes with T&E ranibizumab and aflibercept are likely to be comparable to that of fixed-dosing protocols, whilst using fewer injections. Nevertheless, the reviews are considered to be only low-level evidence to support the applicability of the efficacy outcomes to the Australian setting, and the issue remains that the mean number of injections per patient in the trials is unlikely to be representative of aflibercept utilisation in Australia.

6.10 The brolucizumab dosing regimen used in OSPREY was not completely consistent with the regimen proposed in the draft PI. The submission presented this trial as supportive evidence, as it provided a comparison of brolucizumab 6 mg and aflibercept 2 mg when administered at similar dose intervals up to Week 40 of treatment (q8w following the initial loading doses). The results were consistent with those reported for HAWK and HARRIER.

6.11 The pre-specified non-inferiority margin for the primary outcome of the HAWK and HARRIER trials (change in BCVA from baseline to Week 48) was 4 letters. This non-inferiority margin was reasonable. The PBAC have previously accepted that an improvement in visual acuity of 10 letters represented a clinically important result, although noted that an increase of 5 or more BCVA letters might represent a clinically important difference for some patients, but the clinical importance will also depend on the baseline visual acuity of each eye (Ranibizumab Public Summary Document (PSD), March 2013 PBAC Meeting).

Comparative effectiveness

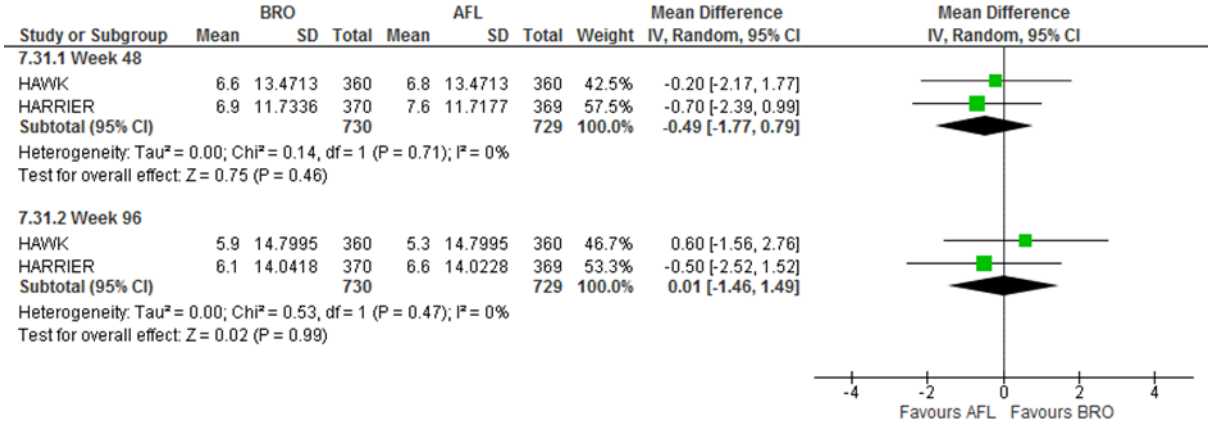
6.12 The results for the primary outcome in HAWK and HARRIER, least squares (LS) mean change in BCVA from baseline to Week 48, as well as the secondary outcome of mean change in BCVA from baseline to Week 96, are summarised below (Table 4), while the forest plots for the meta-analyses of these outcomes are presented in Figure 1.

Table 4: LS mean change in BCVA (letters read) from baseline – FAS, LOCF

	HAWK		HARRIER	
	BRO 6 mg N=360	**AFL 2 mg N=360**	**BRO 6 mg N=370**	**AFL 2 mg N=369**
Mean baseline BCVA, letters (SD)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Change in BCVA (letters) from baseline to 48 weeks				
Mean change, letters (SD)	6.4 (14.4)	7.0 (13.2)	6.9 (11.5)	7.6 (12.5)
Mean LS change, letters (SE)	6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
Mean difference (95% CI)[a]	-0.60 (-2.62, 1.42)		-0.70 (-2.43, 1.03)	
LS mean difference (95% CI)[b]	-0.2 (-2.1, 1.8)		-0.7 (-2.4, 1.0)	
Change in BCVA (letters) from baseline to 96 weeks				
Mean change, letters (SD)	5.6 (15.6)	5.6 (14.8)	6.1 (14.1)	6.6 (14.6)
Mean LS change, letters (SE)	5.9 (0.78)	5.3 (0.78)	6.1 (0.73)	6.6 (0.73)
Mean difference (95% CI)[a]	0.0 (-2.2, 2.2)		-0.50 (-2.56, 1.56)	
LS mean difference (95% CI)[b]	0.5 (-1.6, 2.7)		-0.4 (-2.5, 1.6)	

AFL = aflibercept; BCVA = best corrected visual acuity; BRO = brolucizumab; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.
[a] Calculated *post hoc* in Review Manager 5.3 for this submission.
[b] LS mean difference, as reported in the CSRs for HAWK and HARRIER.
Source: Table 2-17, Section 2 of the submission.

Figure 1: Forest plots of meta-analyses of LS mean change in BCVA from baseline to Week 48 and to Week 96 (FAS-LOCF)



AFL = aflibercept; BCVA = best corrected visual acuity; BRO = brolucizumab; CI = confidence interval; IV = inverse variance; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; SD = standard deviation.
Source: Figure 2-22, Section 2 of the submission

6.13 The lower limit of the 95% confidence interval (CI) of the mean difference between the brolucizumab and aflibercept treatment arms, for the outcomes of mean change in BCVA from baseline to Week 48 and Week 96, was within the pre-specified non-inferiority margin of 4 letters in both the individual trials and the meta-analyses.

6.14 The submission claimed that brolucizumab would provide the benefit of less frequent dosing, while maintaining the same efficacy as aflibercept. The results of a Kaplan-Meier analysis for the time to first q8w treatment need for patients assigned to brolucizumab 6 mg, indicated that the probability of a patient being maintained on a q12w regimen up to Week 44 was 55.6% in HAWK and 51.0% in HARRIER, and had

reduced to 45.4% and 38.6%, respectively, by Week 92 (p108 of the submission; Table 14.2-6.1, p1030 HAWK CSR; Table 14.2-6.1, p819 HARRIER CSR).

6.15 The PBAC agreed with the ESC that the trial design of the HAWK and HARRIER trials was not consistent with Australian clinical practice, and that the trials may not be applicable to the Australian setting.

Comparative harms

6.16 The key safety results are summarised below (Table 5).

Table 5: Summary of key adverse events in the trials (HAWK and HARRIER) at Week 96

	Trial ID	Brolucizumab n/N (%)	Aflibercept n/N (%)	Pooled results	
				RD[a] (95% CI)	RR[b] (95% CI)
Ocular AEs overall					
Any AEs	HAWK	220/360 (61.1%)	201/360 (55.8%)	0.02 [-0.04, 0.08]	1.05 [0.95, 1.16]
	HARRIER	174/370 (47.0%)	176/369 (47.7%)	I^2 = 24% (P = 0.25)	I^2 = 10% (P = 0.29)
AEs resulting in discontinuation	HAWK	[redacted]/360 ([redacted]%)	[redacted]/360 ([redacted]%)	[redacted] [[redacted], [redacted]]	[redacted] [[redacted], [redacted]]
	HARRIER	[redacted]/370 ([redacted]%)	[redacted]/369 ([redacted]%)	I^2 = [redacted]% (P = [redacted])	I^2 = [redacted]% (P = [redacted])
Non-fatal SAEs	HAWK	12/360 (3.3%)	5/360 (1.4%)	**0.02 [0.00, 0.04]**	**2.27 [1.12, 4.58]**
	HARRIER	13/370 (3.5%)	6/369 (1.6%)	I^2 = 0% (P = 0.97)	I^2 = 0% (P = 0.88)
Treatment (procedure)-related non-fatal SAEs[c]	HAWK	[redacted]/360 ([redacted]%)	[redacted]/360 ([redacted]%)	[redacted] [[redacted], [redacted]]	[redacted] [[redacted], [redacted]]
	HARRIER	[redacted]/370 ([redacted]%)	[redacted]/369 ([redacted]%)	I^2 = [redacted]% (P = [redacted])	I^2 = [redacted]% (P = [redacted])
Non-ocular AEs overall					
Any AEs	HAWK	289/360 (80.3%)	303/360 (84.2%)	-0.01 [-0.07, 0.05]	0.99 [0.91, 1.07]
	HARRIER	282/370 (76.2%)	272/369 (73.7%)	I^2 = 56% (P = 0.13)	I^2 = 55% (P = 0.14)
AEs resulting in discontinuation	HAWK	[redacted]/360 ([redacted]%)	[redacted]/360 ([redacted]%)	[redacted] [[redacted], [redacted]]	[redacted] [[redacted], [redacted]]
	HARRIER	[redacted]/370 ([redacted]%)	[redacted]/369 ([redacted]%)	I^2 = [redacted]% (P = [redacted])	I^2 = [redacted]% (P = [redacted])
Non-fatal SAEs	HAWK	85/360 (23.6%)	110/360 (30.6%)	**-0.06 [-0.10, -0.01]**	**0.79 [0.66, 0.95]**
	HARRIER	69/370 (18.6%)	85/369 (23.0%)	I^2 = 0% (P = 0.56)	I^2 = 0% (P = 0.81)
Treatment (procedure)-related non-fatal SAEs[d]	HAWK	[redacted]/360 ([redacted]%)	[redacted]/360 ([redacted]%)	[redacted] [[redacted], [redacted]]	[redacted] [[redacted], [redacted]]
	HARRIER	[redacted]/370 ([redacted]%)	[redacted]/369 ([redacted]%)	I^2 = [redacted]% (P = [redacted])	I^2 = [redacted]% (P = [redacted])
Deaths					
Deaths	HAWK	8/360 (2.2%)	12/360 (3.3%)	-0.01 [-0.02, 0.00]	0.63 [0.31, 1.29]
	HARRIER	4/370 (1.1%)	7/369 (1.9%)	I^2 = 0% (P = 0.84)	I^2 = 0% (P = 0.84)
Specific ocular AEs					
Uveitis	HAWK	8/360 (2.2%)	1/360 (0.3%)	**0.01 [0.00, 0.02]**	**7.65 [1.40, 41.80]**
	HARRIER	3/370 (0.8%)	0/369 (0%)	I^2 = 36% (P = 0.21)	I^2 = 0% (P= 0.94)
Vitreous floater	HAWK	22/360 (6.1%)	16/360 (4.4%)	**0.02 [0.00, 0.04]**	1.83 [0.88, 3.83]
	HARRIER	15/370 (4.1%)	5/369 (1.4%)	I^2 = 0% (P = 0.60)	I^2 = 40% (P = 0.20)
Iritis	HAWK	9/360 (2.5%)	1/360 (0.3%)	0.01 [-0.02, 0.04]	2.19 [0.09, 54.06]
	HARRIER	0/370 (0%)	1/369 (0.3%)	I^2 = 92% (P< 0.001)	I^2 = 66% (P = 0.09)
Retinal pigment epithelial tear[e]	HAWK	12/360 (3.3%)	4/360 (1.1%)	**0.01 [0.00, 0.03]**	2.18 [0.99, 4.79]
	HARRIER	8/370 (2.2%)	5/369 (1.4%)	I^2 = 0% (P = 0.33)	I^2 = 0% (P = 0.43)
Retinal haemorrhage[e]	HAWK	21/360 (5.8%)	20/360 (5.6%)	0.02 [-0.00, 0.03]	1.59 [0.58, 4.34]
	HARRIER	12/370 (3.2%)	4/369 (1.1%)	I^2 = 6% (P = 0.30)	I^2 = 62% (P = 0.11)
Cataract	HAWK	20/360 (5.6)	13/360 (3.6%)	-0.03 [-0.14, 0.07]	0.62 [0.11, 3.65]
	HARRIER	11/370 (3.0%)	43/369 (11.7%)	I^2 = 95% (P< 0.001)	I^2 = 93% (P< 0.001)

AEs = adverse events; CI = confidence interval; n = number of patients experiencing the event; N = total patients in the group; RD = risk difference; RR = risk ratio; SAEs = serious adverse events

Note: Statistically significant differences are presented in bold

[a] Brolucizumab vs. aflibercept. A result of <0 indicates treatment effect favouring brolucizumab.

[b] Brolucizumab vs. aflibercept. A result of <1 indicates treatment effect favouring brolucizumab.

[c] Data on treatment (procedure)-related serious ocular AEs were derived from Table 14.3.1-4.1_Y2, p19585 of the HAWK CSR and Table 14.3.1-4.1_Y2, p13998 of the HARRIER CSR. Pooled RR and RD were calculated during the evaluation using the Stata 14 software.

[d] Data on treatment (procedure)-related serious non-ocular AEs were derived from Table 14.3.1-4.2_Y2, p19590 of the HAWK CSR and Table 14.3.1-4.2_Y2, p14004 of the HARRIER CSR. Pooled RR and RD were calculated during the evaluation using the Stata 14 software

[e] Data on retinal pigment epithelia tear and retinal haemorrhage events were not presented in the submission, but were derived from Table 12-8, p254 of the HAWK CSR and Table 12-8, pp233-234 of the HARRIER CSR. Pooled RR and RD were calculated during the evaluation using the Stata 14 software.

Source: Table 2-31, Table 2-34, Table 2-37, Table 2-46, Table 2-53, Table 2-54, Table 2-55, and Table 2-56, Section 2 of the submission

6.17 The results of the meta-analyses showed that the incidence of total ocular AEs, non-ocular AEs, AEs leading to treatment withdrawal and fatal events was generally comparable between brolucizumab and aflibercept. However, a statistically significantly greater proportion of subjects in the brolucizumab arm experienced serious ocular AEs in the study eye compared with aflibercept at Week 96 (3.4% (25/730) vs. 1.5% (11/729); risk ratio (RR): 2.27 [95% CI: 1.12, 4.58]). Similar results were reported when only drug-related or administration procedure-related serious ocular AEs were considered ([redacted]% ([redacted]730) vs. [redacted]% ([redacted]729); RR: [redacted] [95% CI: [redacted]]). Conversely, patients treated with brolucizumab had a lower incidence of non-ocular SAEs (21.1% (154/730) vs. 26.7% (195/729); RR: 0.79 [95% CI: 0.66, 0.95]). However, the majority of these non-ocular SAEs were assessed by the investigator as unrelated to VEGF therapy. The difference in the rate of treatment (procedure)-related non-ocular SAEs between the two treatment groups did not reach statistical significance.

6.18 There were significantly more uveitis events in the brolucizumab arm compared with the aflibercept arm at Week 96. The pooled risk differences in the rates of vitreous floater and retinal pigment epithelial tear were also marginally statistically significant, favouring aflibercept. The incidence of iritis and retinal haemorrhage was higher in the brolucizumab arm compared with aflibercept in one of the clinical trials, but the rates of these two events were similar in the other trial. The pooled estimates did not reach statistical significance. Results for cataracts were inconsistent between the HAWK and HARRIER trials. No conclusion could be drawn for this outcome.

6.19 The PSCR argued that the rate of ocular SAEs in the brolucizumab arm, while statistically inferior to aflibercept, was low in magnitude and the extent of any inferiority, if it is a real effect, is small. The PSCR stated that the safety profile for brolucizumab could be described as different, but clinically non-inferior. The ESC considered the overall ocular SAE rate with brolucizumab was significant and not non-inferior to aflibercept. The Sponsor stated in the Pre-PBAC response that the majority of the ocular SAEs were assessed by the investigator as mild or moderate, and resolved without sequelae after treatment with topical corticosteroids.

6.20 One fatal event (2.2%) in the brolucizumab 6 mg arm of the OSPREY trial was considered treatment-related. This patient died from ischemic heart disease. The principal investigator assessed this event as serious, severe, and related to brolucizumab, as causality could not be ruled out (OSPREY CSR). The CSR of the HAWK trial also reported one patient (0.3%) receiving brolucizumab 3 mg[†] experienced a serious AE with a fatal outcome (cerebrovascular accident) which was considered to be related to study treatment by the investigator (p267 of the HAWK CSR).

[†] Data from the brolucizumab 3 mg group in HAWK were not included in the submission, as the brolucizumab 3 mg dose will not be registered.

6.21 The PBAC reiterated the safety concerns of the ESC, and considered that the claim of non-inferior safety may not be adequately supported. The PBAC noted the higher incidence of ocular SAEs with brolucizumab (uveitis, vitreous floater, and retinal pigment epithelial tear) and lower incidence of non-ocular SAEs with brolucizumab.

Clinical claim

6.22 The submission described brolucizumab 6 mg as non-inferior in terms of effectiveness and equivalent in terms of safety compared with aflibercept 2 mg.

6.23 The PBAC considered that the claim of non-inferior comparative effectiveness of brolucizumab 6 mg and aflibercept 2 mg, at the doses used in the trials, was reasonable.

6.24 However, the PBAC agreed with the ESC that the applicability of the results to the Australian clinical setting was limited due to the 8-weekly fixed-dosing treatment regimen used for aflibercept (see paragraph 6.9) and the less flexible treatment regimen for brolucizumab compared with its PI (see paragraph 6.8). Additional applicability issues were that not all patients in the HAWK and HARRIER trials had subfoveal CNV lesions (see paragraph 6.16) and patients who had received prior treatment for neovascular AMD were excluded from the brolucizumab trials (see paragraph 2.5).

6.25 The submission's claim that brolucizumab would provide the benefit of less frequent dosing compared with currently available anti-VEGFs, while maintaining the same efficacy, was poorly supported by the evidence given:

- Patients in the aflibercept arm of the trials could not extend the treatment interval beyond q8w; and
- The probability of a patient being maintained on the brolucizumab q12w regimen up to Week 44 of the trials was only 56% in HAWK and 51% in HARRIER.

6.26 The PBAC considered that the non-inferior claim of brolucizumab versus aflibercept in terms of comparative safety was not adequately supported by the clinical evidence:

- Results of meta-analyses of the safety data from the HAWK and HARRIER trials indicated higher rates of ocular SAEs and treatment (procedure)-related ocular SAEs in patients receiving brolucizumab compared with those treated with aflibercept;
- Although the incidence of non-ocular SAEs was lower for brolucizumab than for aflibercept, the majority of these AEs were considered unrelated to study drug or drug administration procedure.

Economic analysis

6.27 The submission presented a cost-minimisation analysis (CMA) of brolucizumab to aflibercept based on direct randomised trials of HAWK and HARRIER. The Commentary

considered it may not be appropriate to conduct a cost-minimisation analysis given brolucizumab may not be non-inferior to aflibercept for safety.

6.28 The equi-effective doses were estimated by the Sponsor as brolucizumab 6 mg [redacted] administrations per year and aflibercept 2 mg [redacted] administrations per year for the maintenance treatment phase. The ESC considered that the HAWK and HARRIER trial designs were likely to have biased the CMA against aflibercept, and that the proposed equi-effective doses are uncertain because they may not be realised in clinical practice. The ESC considered that in clinical practice a 1:1 dose relativity was more likely. In the pre-PBAC response, the Sponsor accepted that the injection frequency ratio of brolucizumab with aflibercept and ranibizumab should be 1:1.

6.29 In its consideration of aflibercept for subfoveal CNV due to AMD, the PBAC considered it was uncertain whether less frequent injections would eventuate with aflibercept treatment compared to ranibizumab treatment, and considered that the number of injections per patient per year for each product is likely to be similar (p3, aflibercept PSD, March 2012 PBAC meeting).

6.30 The submission noted that the prices of aflibercept and ranibizumab had been linked via cost-minimisation since the date of PBS-listing of aflibercept in December 2012. However, since the introduction of F1 anniversary cuts, which apply to individual drugs at different times, the prices of these two agents are no longer the same:

- Aflibercept was subject to a 5% F1 anniversary cut on 1 April 2018;
- Ranibizumab was subject to a 10% F1 anniversary cut on 1 April 2018.

6.31 The submission requested that the listing of brolucizumab be considered under the pricing arrangements outlined in Clause 5.7 of the Strategic Agreement. Specifically, brolucizumab would not be subject to the statutory price reductions that have been applied to the comparator regimens. The PBAC have previously considered that the application of Clause 5.7 of the Strategic Agreement is determined by the Minister (or Delegate), and is not a matter for PBAC (para 6.41, levonorgestrel PSD, March 2019 Meeting). Therefore, this remains for consideration by the Minister (or Delegate). The Sponsor acknowledged that application of the Strategic Agreement is not for PBAC consideration, and it can be determined following a PBAC recommendation on a cost-minimisation basis to either ranibizumab or aflibercept.

6.32 The submission presented two cost-minimised prices of brolucizumab:

- Prior to 30 June 2022: based on the pre-anniversary cut price of aflibercept/ranibizumab, in line with Clause 5.7 of the Strategic Agreement; and
- From 1 July 2022: based on the current weighted average price of aflibercept/ranibizumab. This price will remain current at the expiration of the Strategic Agreement in July 2022.

6.33 A summary of the prices associated with comparator regimens used in the CMA is provided in Table 6 below.

Table 6: Published and effective ex-manufacturer prices used in the cost-minimisation analyses

		Aflibercept[a]	Ranibizumab	Weighted[b]
Listed Price				
A	Pre-anniversary cuts published ex-manufacturer price	$1,036.00	$1,036.00	$1,036.00
B	Anniversary cuts (from April 2018)	5%	10%	
C	Current published ex-manufacturer price	$984.20	$932.40	$962.94
Effective Price				
F	Pre-anniversary cuts effective ex-manufacturer price	$	$	$
G	Anniversary cuts (from April 2018)	5%	10%	
H	Current effective ex-manufacturer price	$	$	$

[a] Since ranibizumab is provided by the same sponsor, it was known by the submission. The submission assumed that the aflibercept effective price is equivalent to ranibizumab at the time of listing

[b] Weighted based on PBS usage statistics for aflibercept (Item 2168D; 58.95%) and ranibizumab (Items 1382R and 10138N; 41.05%) between January and December 2018.

Source: Compiled during the evaluation based on information presented in 'Section 3 model_brolucizumab.xlsx'.

6.34 The submission used the dispensed price for maximum quantity (DPMQ) to calculate the cost-minimised price of brolucizumab. It is noted that pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. The evaluation revised the submission's base case so that the cost-minimisation analysis was performed based on the ex-manufacturer price, rather than the dispensed price.

6.35 The CMA in the submission used the pre-anniversary price cut effective ex-manufacturer price of aflibercept and the current weighted effective price of aflibercept and ranibizumab. The submission proposed an AEMP for brolucizumab of $ until 30 June 2022, based on a dose relativity of (aflibercept): (brolucizumab) and the pre-anniversary price cut of aflibercept/ranibizumab ($). From 1 July 2022, the proposed brolucizumab AEMP was $, based on a dose relativity of : and a weighted aflibercept/ranibizumab price ($).

6.36 The pre-PBAC response provided revised prices assuming a dose relativity of 6.03 (aflibercept) : 6.03 (brolucizumab), corresponding to an AEMP of $ until 30 June 2022 and $ after 1 July 2022. The PBAC considered 1:1 substitution was appropriate.

6.37 As noted in the PBAC Guidelines (2016, v5.0), PBAC is required to consider the effectiveness and cost of the proposed medicine compared with alternative therapies. The Guidelines state that, under the National Health Act 1953, Section 101 (3B), the PBAC cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health. The alternative therapies,

in this case, may include aflibercept and ranibizumab. The PBAC noted that ranibizumab is the lowest cost alternative and advised that the CMA for brolucizumab should be performed against the lowest cost anti-VEGF.

Drug cost/patient/year

6.38 As noted above, the submission proposed two prices of brolucizumab; one that would apply until 30 June 2022, and one that would apply after 1 July 2022.

6.39 Based on the prices in the submission and the pooled average number of doses per year ( ) between Week 48 and Week 92 in the HAWK and HARRIER trials, the total cost of brolucizumab/patient/year in the maintenance phase is as follows.

- For doses dispensed prior to 30 June 2022 using a brolucizumab price of $: drug cost/patient/year=$. Incorporating the cost of administration ($1,547), the total cost is $.
- For doses dispensed after 1 July 2022 using a brolucizumab price of $: drug cost/patient/year=$. Incorporating the cost of administration ($1,547), the total cost is $.

6.40 Based on the prices in the pre-PBAC response and equivalent number of doses per year to aflibercept ( ), the total cost of brolucizumab/patient/year in the maintenance phase is the same as in the submission due to the increased number of doses at a lower price, as follows.

- For doses dispensed prior to 30 June 2022 using a brolucizumab price of $: drug cost/patient/year=$. Incorporating the cost of administration ($1,814), the total cost is $.
- For doses dispensed after 1 July 2022 using a brolucizumab price of $: drug cost/patient/year=$. Incorporating the cost of administration ($1,814), the total cost is $.

6.41 The total cost of aflibercept and ranibizumab per patient per year at the maintenance phase is $. This is based on the pooled average number of doses per year (6.03) between Week 48 and Week 92 in the HAWK and HARRIER trials, and the current weighted effective prices of aflibercept and ranibizumab ($)‡. An additional cost associated with administration would also apply ($1,814), resulting in a total cost of $ per patient per year.

‡ Current ex-manufacturer price of aflibercept ($) and ranibizumab) weighted by the current usage of aflibercept (approximately 58.95%) and ranibizumab (approximately 41.05%). Ex-manufacturer prices of aflibercept and ranibizumab were calculated based on an assumed % rebate, based on the effective price of ranibizumab which is known to the Sponsor.

Estimated PBS usage & financial implications

6.42 This submission was not considered by DUSC. The submission used a market-share approach to predict the likely use and financial impact of listing brolucizumab on the PBS.

6.43 The estimated use and financial implications of listing brolucizumab on the PBS provided in the pre-PBAC response (using the prices proposed in paragraph 6.38 and assuming 1:1 substitution) are summarised below (Table 7).

6.44 The estimated net cost to the PBS/RPBS (and the cost to Government, since the incremental administration cost is zero with 1:1 substitution) for the first three years of proposed listing is $[redacted]; from years 4 to 6, there is a total saving to the government of $[redacted] based on a weighted price of aflibercept and ranibizumab after 30 June 2022.

Table 7: **Estimated use and financial implications provided in pre-PBAC response**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Reduction in the use of other medicines						
Aflibercept, 4 mg/0.1 mL injection (vial) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 1 x 0.165 mL syringe [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 1 x 0.23 mL syringe [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of scripts that will be replaced [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts of brolucizumab dispensed						
Number of brolucizumab scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of brolucizumab						
DPMQ (effective)	$[redacted] [b]		$[redacted] [c]		$[redacted] [d]	
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for ranibizumab and aflibercept						
DPMQ (effective)	Aflibercept (59%: $[redacted]) and Ranibizumab (41%; $[redacted]): Weighted $[redacted]					
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Assuming uptake of [redacted]% in 'new and switch' patients in year 1, increasing to [redacted]% in year two, and a discontinuation rate of [redacted]%, the submission derived the market share of brolucizumab among all patients treated for wet AMD being [redacted]% in Year 1 and [redacted]% in Year 2, and then the submission assumed the uptake of brolucizumab in subsequent years to be [redacted]%, [redacted]%, [redacted]% and [redacted]% in Year 3, Year 4, Year 5 and Year 6, respectively.

[b] Price based on cost-minimisation analysis compared to the effective ex-manufacturer price of aflibercept and ranibizumab before the pre-anniversary price cuts (both: $[redacted]). *This is appropriate if the Minister (or delegate) accepts that Clause 5.7 of the Strategic Agreement is applicable.*

[c] The Strategic Agreement is due to expire on 30 June 2022. The submission assumed that the price of brolucizumab in the first half 2022 would be based on the cost-minimisation analysis using the price of aflibercept and ranibizumab prior to the pre-anniversary statutory price cuts ($[redacted] for both). After 1 July 2022, the price of brolucizumab in the submission was based on the cost-minimisation analysis using the current weighted price of aflibercept and ranibizumab ($[redacted] for aflibercept (assumed); $[redacted] for ranibizumab; weighted based on current usage; $[redacted]). During the calendar year of 2022, the price would be a weighted price for these two periods.

[d] Price based on the cost-minimisation analysis using the current weighted price of aflibercept and ranibizumab ($[redacted]), which will still be applicable at 1 July 2022.

The redacted table shows that at Year 6, the estimated number of scripts was between 100,000 – 200,000 per year and a net saving to the Government would be less than $10 million per year.

6.45 The submission estimated that there would be significant net costs to the PBS/RPBS ($60 - $100M) and to the Government ($30 - $60M) health budgets over 6 years as a result of the PBS listing of brolucizumab, despite a non-inferiority claim of brolucizumab as well as the cost-minimisation approach claimed in the submission. The revised cost estimates provided in the pre-PBAC response alleviated some of the expected costs through the acceptance by the Sponsor of a 1:1 dosing relativity (revised cost to PBS/RPBS and Government=$10 - $20M). Some outstanding issues of concern are:

- The requested price for brolucizumab until the expiration of the Strategic Agreement (30 June 2022, approximately 2.5 years after listing) is based on the price of comparator regimens prior to the F1 statutory price reductions, and is therefore more costly than comparator regimens that have been subject to a 5% (aflibercept) and 10% (ranibizumab) price reduction.
- The requested price for brolucizumab after the expiration of the Strategic Agreement (30 June 2022) is based on the weighted price of aflibercept and ranibizumab according to PBS volumes in 2018. The PBAC considered that the CMA for brolucizumab should be performed against the least expensive anti-VEGF (ranibizumab).

6.46 The derivation of the market shares of brolucizumab among all patients treated for neovascular AMD in Year 3 to Year 6 was not explained by the submission. These estimates appeared lower than would be expected, taking into consideration the assumptions used to estimate the expected uptake in the first two years. Therefore, the cost of brolucizumab to the PBS may have been underestimated by the submission. The PSCR stated the uptake rates used for brolucizumab were based on the experience of aflibercept. However, it should be noted that the estimated proportion of 'new and switch' patients as a total of all patients (as calculated by the submission) was based on a steady state 'new and switch' proportions of patients receiving ranibizumab and aflibercept between 2014 and 2018. The ESC agreed with the evaluation that the submission's estimates were likely to be underestimated.

Financial Management – Risk Sharing Arrangements

6.47 The submission noted that ranibizumab and aflibercept currently have special pricing and risk sharing arrangements in place covering PBS expenditure in relation to the treatment of neovascular AMD. The submission stated that the degree to which these arrangements would, or would not, apply to brolucizumab is not known at this stage.

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

7 PBAC Outcome

7.1 The PBAC did not recommend brolucizumab for the treatment of patients with subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD). The PBAC noted the higher incidence of ocular serious adverse events (SAEs) reported for brolucizumab compared to aflibercept in the clinical studies and considered the claim of non-inferior safety was uncertain.

7.2 The submission nominated aflibercept as the main comparator as it has a higher market share, and ranibizumab as a secondary comparator. The PBAC noted that ranibizumab had become the least costly comparator since the F1 anniversary price reduction applied to ranibizumab (10%) and aflibercept (5%) on 1 April 2018. The PBAC noted that no data were provided demonstrating brolucizumab provides a significant

improvement in efficacy or reduction of toxicity over the alternative therapies (aflibercept and ranibizumab) (paragraph 5.3). The PBAC advised that the drug cost used for the CMA should be the effective ranibizumab price rather than the weighted price of aflibercept and ranibizumab, as ranibizumab is the least costly anti-VEGF agent.

7.3 The PBAC was satisfied that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept, based on the two key trials (HAWK and HARRIER). However, the PBAC considered that the overall ocular SAE rate with brolucizumab (3.4%) was significantly different to aflibercept (1.5%) and the claim of non-inferiority in terms of safety was uncertain. The ocular SAEs that occurred more frequently with brolucizumab included uveitis, vitreous floater and retinal pigment epithelial tear. The PBAC considered that the safety profile of brolucizumab is uncertain compared to its comparators, and there are potential associated cost implications.

7.4 The PBAC did not consider brolucizumab would provide the benefit of less frequent dosing compared with currently available anti-VEGFs (as claimed in the submission), while maintaining the same efficacy, because the dosing regimens for brolucizumab and aflibercept in both HAWK and HARRIER were not as flexible as those specified in the respective PIs. Specifically, the PBAC considered that the results of these trials may not be realised in Australian clinical practice because:

- Patients in the aflibercept arm could not extend treatment intervals beyond 8 weeks;
- The probability of a patient maintaining a 12 weekly dosing regimen for brolucizumab up to Week 44 was only 51-56%, and further reduced by Week 92;
- The treatment regimen for brolucizumab in the trials (q12w with the option of changing to q8w for the remainder of the study) was less flexible than the individualised treatment proposed in the draft PI (q12w with flexibility to treat as often as q8w).

7.5 The PBAC considered that the proposed equi-effective doses of brolucizumab 6 mg x [redacted] per year vs aflibercept 2 mg x [redacted] per year were inappropriate, given the issues described in paragraph 7.4. The PBAC noted that in Australian practice, the 'treat and extend' regimen is expected and should apply to all anti-VEGF injections, and considered that there are no clinical reasons for dosing frequencies amongst them to be different to each other. The PBAC considered that the CMA should assume an identical number of injections (6.03) for aflibercept/ranibizumab and brolucizumab, as it is highly uncertain that there will be any difference in injection frequency between brolucizumab, aflibercept and ranibizumab in clinical practice. The PBAC noted the pre-PBAC response provided revised prices bases on 1:1 substitution (i.e. identical number of injections).

7.6 The PBAC considered that the financial implications were uncertain at the price proposed in the pre-PBAC response. The listing of brolucizumab was not cost neutral to the PBS and was associated with cost implications of a net $10 - $20 million over 6 years, due to (i) the request for the pre-F1 statutory cut comparator price to apply to brolucizumab pre-2022, and (ii) the weighted aflibercept/ranibuzumab price to apply post-2022.

7.7 The PBAC considered that any future submission should address the uncertain claim of non-inferior safety and difference in safety profile through a price reduction against the lowest cost alternative (paragraph 7.2) and assume 1:1 substitution (paragraph 7.5).

7.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.