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

1 Purpose of Application

1.1 This resubmission requested an Authority Required listing for brolucizumab for the treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD) in patients who are non-responsive (ongoing exudation/fluid) despite first-line anti-vascular endothelial growth factor (VEGF) treatment i.e. a second-line listing. Brolucizumab was considered for a first-line listing by the PBAC in November 2019, March 2020 and July 2020.

1.2 The requested listing for second-line use was based on a cost-minimisation analysis of brolucizumab to first-line agents aflibercept (main comparator) and ranibizumab (secondary comparator). The submission incorporated a 5% price reduction for brolucizumab, which was an acknowledgement that there may be uncertain costs in managing brolucizumab-specific safety events in clinical practice. The key components of the clinical issue addressed by the submission are summarised in Table 1.

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

Component	Description
Population	Patients with neovascular (wet) AMD who are non-responsive to prior anti-VEGF therapy
Intervention	Brolucizumab 6 mg every 4 weeks for the first three doses, with subsequent treatment every 8 or 12 weeks, dependent on disease activity as assessed by visual acuity and/or anatomical parameters.
Comparators	Main comparator: Aflibercept 2 mg every month for three months, followed by treatment every two months (treatment may continue every two months or be adjusted to longer intervals between treatments based on the physician's judgement of visual and/or anatomic outcomes. Treatment intervals greater than four months (16 weeks) between injections have not been studied). Secondary comparator: Ranibizumab 0.5 mg every 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.
Outcomes	Anatomical changes: Reduction of disease activity at 16 weeks and change from baseline in Central Subfield Thickness Functional changes: Visual acuity Adverse events
Clinical claim	Brolucizumab is superior in terms of efficacy and marginally inferior in terms of safety compared to VEGF inhibitors aflibercept and ranibizumab when used to treat patients with wet AMD who are non-responsive to prior anti-VEGF.

AMD = age-related macular degeneration, VEGF = vascular endothelial growth factor
Source: Table 1.1 of the resubmission

2 Requested listing

2.1 The requested listing is provided below. Suggested additions are in italics and deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
BROLUCIZUMAB solution for intravitreal injection 19.8 mg in 0.165 mL syringe	1	1	2	$1,042.89 (published) $[redacted] (effective)	Beovu® Novartis Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing ☒~~Authority Required – Telephone/Electronic/Emergency~~ ☐Authority Required – Streamlined
Indication: Subfoveal choroidal neovascularisation (CNV)
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be due to age-related macular degeneration (AMD)
AND
Clinical criteria:
The condition must be diagnosed by optical coherence tomography; or
The condition must be diagnosed by fluorescein angiography
AND
Clinical criteria:
~~*Patient must have persistent macular exudation, as determined clinically and/or on OCT or FA, despite 6 months of treatment with VEGF inhibitors administered at intervals ≤ 8 weeks*~~ *Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of treatment with either: 1. Aflibercept or 2. Ranibizumab.*
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Patient has not received PBS-subsidised treatment with this drug for this condition for the same eye
AND
Treatment criteria:
Must be treated by an ophthalmologist or *by an accredited ophthalmology registrar* in consultation with an ophthalmologist
Prescribing Instructions: Authority approval for initial treatment of each eye must be sought.
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~~ 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: *Any queries concerning the arrangements to prescribe may be directed to the Services Australia 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 Services Australia website at 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*
Administrative Advice: No increase in the maximum number of repeats may be authorised
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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*
Administrative Advice: Special Pricing Arrangements apply

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Authority Required – Streamlined
Indication: Subfoveal choroidal neovascularisation (CNV)
Treatment Phase: Continuing treatment
Clinical criteria:
The condition must be due to age-related macular degeneration (AMD)
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have previously been granted an authority prescription for the same eye
AND
Treatment criteria:
Must be treated by an ophthalmologist or *by an accredited ophthalmology registrar* in consultation with an ophthalmologist
Administrative Advice: ~~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)~~ *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*
Administrative Advice: No increase in the maximum number of repeats may be authorised
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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*

Administrative Advice: Special Pricing Arrangements apply

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing ☒~~Authority Required – Telephone/Electronic/Emergency~~ ☐Authority Required – Streamlined
Indication: Subfoveal choroidal neovascularisation (CNV)
Treatment Phase: Grandfather
Clinical criteria:
The condition must be due to age-related macular degeneration (AMD)
AND
Clinical criteria:
The condition must be diagnosed by optical coherence tomography; or
The condition must be diagnosed by fluorescein angiography
AND
Clinical criteria:
Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of treatment with either: 1. Aflibercept or 2. Ranibizumab.
AND
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Treatment criteria:
Must be treated by an ophthalmologist or *by an accredited ophthalmology registrar* in consultation with an ophthalmologist
Prescribing Instructions: *A patient may qualify for PBS-subsidised treatment under this restriction once only per eye.*
Prescribing Instructions: *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.*
~~**Prescribing Instructions:**~~ ~~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)~~
Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to the Services Australia 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 Services Australia website at 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*
Administrative Advice: No increase in the maximum number of repeats may be authorised
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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*
Administrative Advice: Special Pricing Arrangements apply

2.2 The Sponsor requested a special pricing arrangement (SPA) for brolucizumab with an effective dispensed price of $[redacted].

2.3 The requested listing is a subset of the registered TGA indication because (1) it restricts eligibility to patients with subfoveal CNV, whereas the TGA indication is for the treatment of neovascular AMD, irrespective of the location of the CNV, and (2) it only allows use in patients with persistent macular exudation despite 6 months of treatment with VEGF inhibitors.

2.4 While the Sponsor stated that the premise of their current resubmission is to seek PBS listing as a second-line therapy for a patient population who are non-responsive to first-line treatment for wet AMD, use of brolucizumab following both aflibercept and ranibizumab (i.e. third-line use) has not been excluded in the requested listing. The PBAC considered it would be reasonable for brolucizumab to be used second-line or third-line.

2.5 The resubmission requested a grandfather restriction; however, this restriction did not require that patients must have previously received aflibercept and/or ranibizumab. The ESC and the PBAC considered it would only be appropriate for patients receiving brolucizumab as a second- or subsequent-line treatment in the access program to be transitioned to PBS-subsidised treatment and the grandfather restriction should reflect this.

2.6 The PBAC indicated there may be flow-on changes required to the restrictions for ranibizumab and aflibercept in CNV due to AMD, to recognise switching between VEGF inhibitors.

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

3 Background

Registration status

3.1 Brolucizumab was TGA registered for the treatment of neovascular (wet) AMD on 16 January 2020. On 25 June 2020 the TGA approved updated safety related information in the brolucizumab Product Information regarding reported cases of retinal vasculitis (RV) and retinal vascular occlusion (RVO).

Previous PBAC consideration

3.2 In November 2019, the PBAC did not recommend brolucizumab noting:

- The pivotal clinical studies (HAWK and HARRIER) demonstrated non-inferior efficacy for brolucizumab compared to the main comparator aflibercept. However, a higher incidence of ocular serious adverse events for brolucizumab compared to aflibercept resulted in the claim of non-inferior safety being uncertain. Consequently, the cost-minimisation analysis (CMA) of brolucizumab compared to aflibercept may not have been appropriate (Brolucizumab Public Summary Document (PSD) November 2019, paragraph 6.27).
- Brolucizumab would not provide the benefit of less frequent dosing compared with currently available VEGFs inhibitors, as claimed by the Sponsor (Brolucizumab PSD November 2019, paragraph 7.4).

3.3 In March 2020 the PBAC did not recommend brolucizumab and observed that:

- In addition to the original concerns of the non-inferior safety claim for brolucizumab, there were anecdotal reports from the American Society of Retinal Specialists (ASRS) of retinal artery occlusion and intraocular inflammation occurring in patients following use of brolucizumab in the United States (Brolucizumab PSD March 2020, paragraph 6.2).
- As there were two safe and efficacious treatment options available, the need for additional treatment options was considered low, particularly one with uncertain comparative safety (Brolucizumab PSD March 2020, paragraph 6.4).

3.4 In July 2020 the PBAC again did not recommend brolucizumab and noted:

- Consumer comments stated that an alternative to the two currently available VEGF inhibitors in the case of non-responsiveness would be useful. "However, the PBAC considered that would mean brolucizumab would be second-line therapy, used after failure of the first-line agents (ranibizumab and aflibercept)" (Brolucizumab PSD July 2020, paragraph 6.2).
- The Global Novartis Ophthalmology report identified an emerging new safety signal of RV/RVO with or without presence of intraocular inflammation that may result in severe vision loss associated with brolucizumab (Brolucizumab PSD July 2020, paragraph 6.3).
- The claim of non-inferior safety was not adequately demonstrated and brolucizumab is likely inferior to aflibercept in terms of comparative safety (Brolucizumab PSD July 2020, paragraph 6.4).

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
PBS indication	The PBAC considered that if brolucizumab were to be used in cases of non-responsiveness as suggested in consumer comments, brolucizumab would be second line therapy. (Brolucizumab PSD July 2020, paragraph 6.2)	The requested indication is for subfoveal CNV due to AMD in patients who are non-responsive to prior anti-VEGF treatment.
Safety	Safety concerns regarding newly identified adverse events RV and RVO with or without presence of intraocular inflammation. (Brolucizumab PSD July 2020, paragraph 6.3)	The resubmission: (1) provided additional reports of RV and RVO from a post hoc review of the HAWK and HARRIER clinical trials, (2) provided details of the TGA approved safety update and the TGA mandated training program for ophthalmologists regarding RV and RVO, and (3) proposed a 5% price reduction relative to the lowest cost comparator, stating "The savings associated with this 5% price reduction will outweigh the cost implications of the small increase (~2 %) in the rate of… RV/RVO which occurs in less than 4 % of patients." (Executive summary of the resubmission)
Safety	The claim of non-inferior safety was not adequately demonstrated and that brolucizumab is likely inferior to aflibercept in terms of comparative safety. (Brolucizumab PSD July 2020, paragraphs 6.1 and 6.4)	The resubmission claims that brolucizumab is "marginally inferior" in terms of safety compared to aflibercept and ranibizumab.

RV = retinal vasculitis; RVO = retinal vascular occlusion
Source: Brolucizumab Public Summary Document July 2020; Section 1.1.3 of the submission

4 Population and disease

4.1 AMD is a chronic eye disease characterised by progressive degenerative abnormalities in the central retina (macula) and is a leading cause of severe vision loss and legal blindness in people aged over of 65 years. When AMD progresses to the late stage it can be either non-neovascular (atrophic) 'dry' form or neovascular (exudative) 'wet' form. Neovascular (wet) AMD is characterised by CNV whereby new blood vessels grow beneath or within 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.

4.2 The standard treatment in Australian clinical practice is intravitreal injection with an anti-VEGF agent, generally ranibizumab or aflibercept. Although many eyes with wet AMD respond well following use of one anti-VEGF agent, some patients remain "non-responders" and continue to have recurrent or persistent exudation. Currently patients may switch from aflibercept to ranibizumab or vice versa if they continue to have symptoms of wet AMD following treatment with one anti-VEGF agent.

4.3 This resubmission requested listing of brolucizumab for the treatment of subfoveal CNV due to AMD in patients who have persistent macular exudation despite 6 months of treatment with anti-VEGF therapy. This requested listing differs from the previous

brolucizumab submission/resubmissions, which did not specify that prior anti-VEGF therapy was required.

5 Comparator

5.1 The submission nominated aflibercept as the main comparator and ranibizumab as a secondary comparator. These were the same comparators nominated in the previous submission/resubmissions for first-line treatment. Aflibercept and ranibizumab may not be the appropriate comparators for second-line treatment of wet AMD. Although the current PBS listings do not preclude sequential use of aflibercept followed by ranibizumab or vice versa, the safety, effectiveness and cost-effectiveness of aflibercept and ranibizumab in the second-line setting is uncertain. Thus, placebo for no treatment may be an appropriate comparator in a pre-treated population who remain inadequately- or non-responsive following treatment with either or both aflibercept and ranibizumab. However, the ESC and the PBAC noted the prior DUSC review and other studies, which indicated that switching between anti-VEGF treatments for inadequate- or non-response is common and well established, despite anti-VEGF treatments not being formally evaluated for cost-effectiveness in second- or subsequent-line therapy.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The Sponsor requested a hearing for this item. The clinician stated that, in general, 20-25% of patients have persistent fluid and are relatively injection intensive, requiring treatment at 4-5 week intervals to obtain good clinical outcomes in terms of retaining vision. The clinician emphasised that if patients miss their appointments due to high treatment burden, increased fluid activity occurs leading to permanent vision loss, and that a second- or third-line agent would be useful for injection intensive patients. The clinician noted specifically in relation to brolucizumab that while a slightly more detailed examination is required to detect intraocular inflammation, the risk for inflammation with brolucizumab was low and treatment is straightforward. The PBAC considered that the hearing was not particularly informative, as it did not add substantively to the evidence presented in the submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health care professional (HCP) via the Consumer Comments facility on the PBS website. The HCP commented that brolucizumab is successful as a rescue treatment for patients who fail on aflibercept or ranibizumab, and that it allows for fewer injections compared to those agents. The HCP acknowledged a small number of side effects with brolucizumab, in particular occlusive vasculitis, and proposed that it could be restricted to ophthalmologists with retinal fellowship training so that inflammatory eye complications could be identified early.

Clinical trials

6.3 The resubmission was based on two head-to-head randomised trials comparing brolucizumab 6 mg to aflibercept 2 mg in treatment naïve patients with wet AMD [HAWK (n=720) and HARRIER (n=739)]. These were the pivotal trials presented in the previous brolucizumab submission and resubmissions in the first-line setting.

6.4 No head-to-head randomised trials comparing brolucizumab to aflibercept or ranibizumab in patients with wet AMD who are non-responsive to prior anti-VEGF therapy were identified. Consequently, three non-randomised single-arm studies reported by Avaylon et al. 2020, Sharma et al. 2020 and London et al. 2020 were included in the resubmission to inform using brolucizumab in the second-line setting.

6.5 Details of the trials identified during the evaluation as being of interest in demonstrating the efficacy and safety of brolucizumab are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol/Publication title	Publication citation
Brolucizumab first-line studies		
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 degeneration.	December 2018
HAWK and HARRIER	Hamilton et al. 2020 Disease activity assessments with brolucizumab vs aflibercept in patients with neovascular age related macular degeneration in HAWK and HARRIER.	Abstract presented at Euretina 2020
Brolucizumab switch studies		
Avaylon et al. 2020	Avaylon J, Lee S, Gallemore RP. Case Series on Initial Responses to Intravitreal Brolucizumab in Patients with Recalcitrant Chronic Wet Age-Related Macular Degeneration.	*Int Med Case Rep J*. 2020 May 11;13:145-152.
Sharma et al. 2020	Sharma A, Kumar N, Parachuri N, et al. Brolucizumab-early real-world experience: BREW study.	*Eye* (Lond). 2020 Jul 24. doi: 10.1038/s41433-020-1111-x. Online ahead of print.
London et al. 2020	London N, Khanani A, Thompson M, et al. Treating Neovascular AMD patients with Brolucizumab: A Real-World Study.	Presented at the ASRS conference in July 2020.

Source: Tables 2-5, p 59 of the resubmission.

6.6 The key features of these randomised trials and single arm studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N[a]	Design/duration	Risk of bias	Patient population	Outcomes
Brolucizumab vs. aflibercept (treatment naïve patients with wet AMD) – randomised first-line studies					
HAWK	720[b]	R, DB 96 weeks	Unclear	Patients with CNV due to AMD, treatment naive	Change in BCVA, change in CSFT, DA
HARRIER	739	R, DB 96 weeks	Low	Patients with CNV due to AMD, treatment naive	Change in BCVA, change in CSFT, DA
Meta-analysis	1459	Included HAWK and HARRIER			Change in BCVA, change in CSFT, DA
Second-line use of brolucizumab – non-randomised switch studies					
Avaylon et al. 2020	6	NRD, OL 4 weeks	High	Patients with CNV due to AMD, first-line treatment failure	BCVA, CMT, APT
Sharma et al. 2020	42	NRD, OL Mean 7.2 weeks	High	Patients with CNV due to AMD, previously treated with anti-VEGF treatment	BCVA, CSFT, SRF, IRF
London et al. 2020	282	NRD, OL NR	High	Patients with CNV due to AMD, previously treated with anti-VEGF treatment (93%)	IRF, SRF, PED, ETDRS letter score, CSFT

AMD = age-related macular degeneration; APT = average pericentral thickness; BCVA = best corrected visual acuity; CMT = central macular thickness; CNV = choroidal neovascularisation; CSFT = central subfield thickness; DA = disease activity; DB = double blind; ETDRS = Early Treatment Diabetic Retinopathy Study; IRF = intra-retinal fluid; NR = not reported; NRD = not randomised; OL = open label; PED = pigment epithelial detachment thickness; R = randomised; SRF = sub-retinal fluid

[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 of brolucizumab (3 mg and 6 mg) with aflibercept 2 mg. The total number of patients in all three arms was 1078 (FAS)

Source: Table 3, brolucizumab PSD, November 2019; Avaylon et al. 2020, Sharma et al. 2020, London et al. 2020

6.7 The resubmission stated that the key evidence for brolucizumab versus aflibercept was based on the meta-analysis of the HAWK and HARRIER trials, using secondary efficacy endpoints of anatomic criteria. However, these trials were conducted exclusively in a treatment naïve population while the requested listing is for patients who have previously received at least 6 months of treatment with VEGF inhibitors.

6.8 While the brolucizumab switch studies provide data to demonstrate use of brolucizumab in patients who switch from another anti-VEGF treatment, these studies were non-comparative and reported limited detail. Consequently, the evaluation considered there are no comparative data to demonstrate use of brolucizumab versus aflibercept or ranibizumab in the patient population for which listing is requested. The Sponsor stated in the Pre-Sub-Committee Response (PSCR) that, while the data were limited, the brolucizumab switch studies showed improvements in anatomical measures [from baseline] in over 300 patients. The switch studies were considered by the ESC and the PBAC to be at high risk of bias and low quality evidence, but in conjunction with biological plausibility arguments and the first-line anatomic data, provided limited support of brolucizumab in the requested setting.

Comparative effectiveness

6.9 The results for the HAWK and HARRIER trials presented in the resubmission have been presented previously and remain unchanged. At their meeting in November 2019, the PBAC was satisfied that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept in the first-line setting, based on the primary outcome of mean change in BCVA from baseline to Week 48 from the HAWK and HARRIER trials (Brolucizumab PSD November 2019, paragraph 7.3).

6.10 In this resubmission, however, the secondary outcomes change in central subfield thickness (CSFT) and disease activity (DA) were presented rather than the primary outcome of the trials, best corrected visual acuity (BCVA).

6.11 Details of the mean change in CSFT from baseline from HAWK and HARRIER are provided in Table 5.

Table 5: LS mean change in CSFT from baseline, HAWK and HARRIER (FAS-LOCF)

Trial	Brolucizumab 6 mg		Aflibercept 2 mg		Brolucizumab vs Aflibercept	
	N	LS Change (mean±SE)	N	LS Change (mean±SE)	LS Mean difference (95% CI)	p-value[a]
Time point: Week 48						
HAWK	360	-172.8 (6.70)	360	-143.7 (6.70)	**-29.0 (-47.6, -10.4)**	0.0023[b]
HARRIER	370	-193.8 (6.84)	369	-143.9 (6.84)	**-49.9 (-68.9, -30.9)**	<0.0001
Meta-analysis					**-39.4 (-59.8, -19.0)**	
Heterogeneity: I^2, p-value					58% (p=0.12)	
Time point: Week 96						
HAWK	360	-174.8 (7.27)	360	-148.7 (7.27)	**-26.0 (-46.2, -5.9)**	0.0115
HARRIER	370	-197.7 (6.97)	369	-155.1 (6.98)	**-42.6 (-62.0, -23.3)**	<0.0001
Meta-analysis					**-34.6 (-50.8, -18.4)**	
Heterogeneity: I^2, p-value					25% (p=0.25)	

CI = confidence interval; CSFT = central subfield thickness; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; SE = standard error

[a] 2-sided p-values.

[b] 1-sided p-value 0.0012. For this endpoint, the pre-specified 1-sided alpha for confirmatory testing of superiority was set at 0.005 within the hierarchical testing approach.

Statistically significant differences are bolded.

Source: Table 2-20 and Table 2-21, pp93 of the resubmission

6.12 DA assessments[1] in HAWK and HARRIER at Week 16 allowed for a head-to-head comparison between treatment arms related to 8-weekly or 12-weekly treatment need after 3 monthly loading doses. The results of the meta-analysis found significantly fewer subjects in the brolucizumab arms of HAWK and HARRIER as having a 8-weekly treatment need at Week 16 compared with aflibercept (23.4% vs. 33.3%; RR: 0.70, 95%CI: 0.59, 0.83, p<0.05).

6.13 The non-comparative brolucizumab switch studies all reported limited efficacy data making it difficult to present quantitatively. London et al. (2020) reported a mean

[1] Disease activity was measured using the following guidance criteria:

anatomical central retinal thickness (CRT) reduction of 42.6 µm in the 282 patients who switched to brolucizumab, and that the percentage of patients with intra-retinal fluid (IRF), sub-retinal fluid (SRF) and pigment epithelial detachment thickness (PED) was reduced by 7.3%, 18.2% and 5.2%, respectively. The ESC acknowledged that while the data provided were limited (paragraph 6.8), a proportion of patients may see an improvement after switching to brolucizumab, although considered that the proportion receiving benefit, and the degree of benefit, was highly uncertain.

6.14 While statistically significant results were observed for both change in CSFT and DA in the HAWK and HARRIER trials, no detail of the translation of the comparative treatment effects of these surrogate measures to target clinical outcomes were included in the resubmission. The Sponsor discussed the biologic plausibility of the impact of retinal anatomy changes on vision outcomes in the PSCR (paragraph 6.20).

Comparative harms

6.15 The resubmission provided a post hoc review of HAWK and HARRIER, a review of published literature, and documentation of over 40 cases of the safety events of interest and real world outcomes from the IRIS database in non-responsive wet AMD patients who switched from existing anti-VEGF treatment to brolucizumab. The Sponsor reported that:

- Brolucizumab is associated with a new event, RV/RVO, which typically presents within two months of starting intravitreal brolucizumab.
- A post hoc unmasked review of the intraocular events in HAWK and HARRIER showed the rate of RV was 3.3% and the rate of RV with RVO was 2.1% (which aligns with the increased risk of ocular serious adverse events (SAEs) reported to the PBAC previously).
- The treatment and management proposed by the independent expert panel was clinical examination and imaging to confirm RV/RVO followed by treatment, which was predominantly steroid treatment.
- Most patients that experienced RV/RVO switched to an alternative anti-VEGF agent after resolution of the event without further sequelae.
- The clinical experts found no association between the occurrence of RV/RVO and the previous anti-VEGF or combination of anti-VEGF treatments used (i.e. the events that occurred in patients who switched from either ranibizumab, aflibercept or bevacizumab to brolucizumab).

- Decrease in BCVA of ≥5 letters compared with baseline;
- Decrease in BCVA of ≥3 letters and CSFT increase ≥75 µm compared with Week 12;
- Decrease in BCVA of ≥5 letters due to wet AMD DA compared with Week 12; or
- New or worse IRF/intraretinal cysts compared with Week 12.

6.16 The TGA have reviewed the safety assessment report regarding the emergence of cases of RV/RVO following treatment with brolucizumab and approved the related changes to the brolucizumab Product Information, as well as the risk management activities proposed by the Sponsor. An ophthalmologist targeted educational campaign began early July 2020 with the supply of brolucizumab through a product familiarisation program in Australia on the 6th July 2020.

Benefits/harms

6.17 A summary of the comparative benefits and harms for brolucizumab versus aflibercept is presented in Table 6. These results are from the HAWK and HARRIER trials, which were conducted in treatment naïve patients with wet AMD.

Table 6: Summary of comparative benefits and harms for brolucizumab and aflibercept

Benefits							
Continuous outcome: LS mean change in BCVA (letter read) from baseline, week 48 (primary endpoint)							
Trial	**brolucizumab**			**aflibercept**			**LS mean difference: brolucizumab vs aflibercept (95% CI)**
	N	**LS mean change**	**SE**	**N**	**LS mean change**	**SE**	
HAWK	360	6.6	0.71	360	6.8	0.71	-0.2 (-2.1, 1.8)
HARRIER	370	6.9	0.61	369	7.6	0.61	-0.7 (-2.4, 1.0)
Continuous outcome: LS mean change in CSFT (micrometre) from baseline (FAS-LOCF), week 48 (secondary outcome)							
Trial	**brolucizumab**			**aflibercept**			**LS mean difference: brolucizumab vs aflibercept (95% CI)**
	N	**LS mean change**	**SE**	**N**	**LS mean change**	**SE**	
HAWK	360	-172.8	6.70	360	-143.7	6.70	-29.0 (-47.6, -10.4)
HARRIER	370	-193.8	6.84	369	-143.9	6.84	-49.9 (-68.9, -30.9)

Dichotomous outcome: Disease activity, week 16 (secondary outcome)					
Trial	**brolucizumab n/N**	**aflibercept n/N**	**Relative risk (95% CI)**	**Event rate/100 patients**	
				brolucizumab	**aflibercept**
HAWK	83 / 346 (23.99%)	119 / 344 (34.59%)	0.69 (0.55, 0.88)	24.0	34.6
HARRIER	83 / 364 (22.80%)	115 / 358 (32.12%)	0.71 (0.56, 0.90)	22.8	32.1

Harms						
Trial	**brolucizumab n/N**	**aflibercept n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				brolucizumab	**aflibercept**	
Adverse event: Non-fatal ocular SAEs, week 96						
HAWK	12/360 (3.3%)	5/360 (1.4%)	2.40 (0.85,6.74)	3.3	1.4	0.02 (0.00,0.04)
HARRIER	13/370 (3.5%)	6/369 (1.6%)	2.16 (0.83, 5.62)	3.5	1.6	0.02 (0.00, 0.04)

BCVA = best corrected visual acuity; CI = confidence interval; CSFT = central subfield thickness; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; RD = risk difference; RR = relative risk; SAEs = serious adverse events; SE = standard error.

Source: Tables 2-20 and 2-22 of the resubmission, Tables 2-17 and 2-37 from the original brolucizumab submission (November 2019)

6.18 The non-comparative brolucizumab switch studies provided limited efficacy and safety data.

6.19 On the basis of the limited data presented for brolucizumab in the second- and third-line population, the ESC considered that no conclusions could be made from these data as to comparative efficacy or safety.

Clinical claim

6.20 A claim of "superiority in terms of efficacy is made based on anatomical benefits of brolucizumab compared with aflibercept or ranibizumab within a subgroup of patients with subfoveal choroidal neovascularisation due to age-related macular degeneration that are non-responsive to existing anti-VEGF agents" was not supported by the resubmission.

- The HAWK and HARRIER trials were conducted in patients with wet AMD who were treatment naïve and were therefore not conducted in the patient population for which listing of brolucizumab has been sought. No comparative evidence was provided for patients in the second-line setting.
- The clinical claim was based on the clinical endpoints change in CSFT (week 48) and DA (week 16). These were secondary outcomes from the HAWK and HARRIER trials. While statistically significant results were observed for both change in CSFT and DA, no detail of the translation of the comparative treatment effects of these surrogate measures to target clinical outcomes were included in the resubmission. The PSCR stated that the biologic plausibility of the impact of retinal anatomy changes on vision outcomes is well known, as fluid leaking from the neovascular complex distorts the retinal cells and leads to the typical vision changes seen in patients with wet AMD. The Sponsor further argued that there is international agreement that achieving the goal of wet AMD treatment requires drying the retina; that is, reducing fluid and DA, as measured using functional and anatomic parameters such as CSFT, IRF, SRF and sub-RPE. The Sponsor stated that the translation of the comparative treatment effects of the surrogate anatomical measures to target clinical outcomes has been demonstrated in before and after trials, as summarised in the meta-analyses discussed in the resubmission.
- In both the HAWK and HARRIER trials, brolucizumab met the primary endpoint of non-inferiority in change in BCVA from baseline to Week 48 compared with aflibercept.
- The clinical claim in the resubmission differed from that provided in the previous submissions for brolucizumab, which described brolucizumab 6 mg as non-inferior in terms of effectiveness and equivalent in terms of safety compared with aflibercept 2 mg.
- This claim is in contrast to the view of the PBAC when they evaluated brolucizumab in November 2019, where "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)" (Brolucizumab PSD November 2019, paragraph 7.3). The

PSCR stated that the clinical claim related to a different position for brolucizumab in the treatment algorithm i.e. patients who fail to achieve the optimal response to first line anti-VEGF therapy. However, the ESC and the PBAC noted that the clinical trial evidence presented in the resubmission was again from the HAWK and HARRIER trials in treatment naïve patients, and non-inferiority with respect to effectiveness was previously accepted based on these trials.

6.21 Non-comparative data investigating patients who received brolucizumab after switching from another anti-VEGF treatment were considered by the PBAC to provide only limited supportive information.

6.22 A claim of "marginally inferior in terms of safety compared to VEGF inhibitors aflibercept and ranibizumab when used to treat patients with wet AMD who are non-responsive to prior anti-VEGF" was made in the resubmission. The PBAC has previously noted concerns regarding the safety of brolucizumab in each of the previous submissions/resubmissions, stating that "brolucizumab is likely inferior to aflibercept in terms of comparative safety" (Brolucizumab PSD July 2020, paragraph 6.4). The ESC noted that these issues of comparative safety remain pertinent as the resubmission presented aflibercept as the main comparator.

6.23 The PBAC agreed with the ESC that the claim of superiority based on anatomic secondary endpoints was not adequately supported; however, it considered that non-inferiority in the second-line setting may be reasonable.

6.24 The PBAC agreed with the ESC that the claim of marginally inferior safety was reasonable.

Economic analysis

6.25 The resubmission presented a cost-minimisation analysis of brolucizumab compared with aflibercept primarily based on the direct randomised trials of HAWK and HARRIER that were conducted in treatment naïve patients, using an assumed effective price for aflibercept ($[redacted]). The cost-minimisation analysis incorporated an additional 5% price reduction (to $[redacted]) in acknowledgement that there may be uncertain costs in managing brolucizumab-specific safety events in clinical practice relative to the costs calculated from the trial evidence.

6.26 The equi-effective doses are estimated as 1:1 for brolucizumab 6 mg and aflibercept 2 mg (or ranibizumab 1.65 mg). This was in line with previous advice from the ESC and the PBAC (Brolucizumab PSD November 2019, paragraph 7.7). The ESC considered that a 1:1 ratio for the equi-effective doses was appropriate in the absence of evidence to demonstrate that dosing would be different in second-line compared to first-line use.

6.27 The resubmission stated additional costs for the treatment of RV/RVO and for three additional ophthalmologist visits were expected to be incurred to manage brolucizumab-specific safety events in clinical practice. The ESC considered that the resubmission may have significantly underestimated the cost of treating RV/RVO as it

did not account for steroid therapy, any long term follow up required or possible vitrectomy or panretinal photocoagulation.

Drug cost/patient/year (effective)

6.28 The total drug cost for brolucizumab per patient per year is $[redacted] for the first year of treatment, based on 11.2 doses per year (DUSC review 2018, average figure for switch population Year 1 and includes the loading doses). This compares to a drug cost for ranibizumab of $[redacted], based on 11.2 doses per year (using the effective price for ranibizumab).

6.29 The total cost of brolucizumab per patient per year is $[redacted] for subsequent years of treatment, based on the 8.9 doses per year (DUSC review 2018, average figure for switch population years 2+). This compares to a drug cost for ranibizumab of $[redacted], based on 8.9 doses per year (using the effective price for ranibizumab).

Estimated PBS usage & financial implications

6.30 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the likely predicted use and financial impact of listing brolucizumab on the PBS for patients with subfoveal CNV due to AMD.

6.31 The Sponsor based their estimates on 2 subpopulations: the annual switch population from the 10% PBS sample (those patients who switch from ranibizumab to aflibercept or vice versa); and the treated prevalent population (all treated patients, less switchers and discontinuers, who have active disease after 3 years). The Sponsor used an uptake rate of 30% (Year 1), 40% (Year 2), 50% (Year 3), and 60% for Years 4, 5 and 6. The PBAC considered there were issues with the internal and external validity of the resubmission's estimates of prevalent patients and the uptake rates applied were uncertain.

6.32 The estimated use and financial implications of listing brolucizumab on the PBS are summarised in Table 7.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total no. of patients treated (initiating + continuing)	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed[a]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Estimated financial implications of brolucizumab						
PBS/RPBS cost (effective) [b,c]	$[redacted][11]	$[redacted][12]	$[redacted][13]	$[redacted][14]	$[redacted][15]	$[redacted][16]
Estimated financial implications for other medicines						
Changes in script numbers[a]:						
Ranibizumab 1382R/10138N	-[redacted][2]	-[redacted][7]	-[redacted][8]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Aflibercept 2168D/12152N	-[redacted][6]	-[redacted][3]	-[redacted][9]	-[redacted][10]	-[redacted][10]	-[redacted][4]
Total	-[redacted][8]	-[redacted][10]	-[redacted][5]	-[redacted][5]	-[redacted][5]	-[redacted][5]
PBS/RPBS cost (effective) [b,c]	-$[redacted][11]	-$[redacted][12]	-$[redacted][13]	-$[redacted][14]	-$[redacted][15]	-$[redacted][16]
Net financial implications						
Net cost to PBS/RPBS (effective)[b,c]	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]	-$[redacted][18]	-$[redacted][18]
Net cost to MBS	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]

[a] Assuming 11.2 scripts per year (year 1) and 8.9 scripts per year (subsequent years) for brolucizumab; 9.2 scripts per patient per year for ranibizumab, aflibercepts estimated by the submission.
[b] Less co-payment
[c] Effective price for brolucizumab
Source: Tables 4.5, 4.7, 4.9, 4.11, 4.12, 4.13, 4.14, 4.15, pp145-151 of the resubmission
The redacted values correspond to the following ranges:
[1]5,000 to <10,000
[2]10,000 to <20,000
[3]50,000 to <60,000
[4]90,000 to <100,000
[5]100,000 to <200,000
[6]20,000 to <30,000
[7]30,000 to <40,000
[8]40,000 to <50,000
[9]60,000 to <70,000
[10]80,000 to <90,000
[11]$30 million to <$40 million
[12]$50 million to <$60 million
[13]$70 million to <$80 million
[14]$80 million to <$90 million
[15]$90 million to <$100 million
[16]$100 million to <$200 million
[17]$0 to <$10 million
[18]net cost saving

6.33 The resubmission indicated that approximately 500 to <5,000 patients would be treated with brolucizumab under a patient familiarisation programme (PFP) prior to listing. The ESC noted that the PFP does not require that patients had prior therapy with aflibercept and/or ranibizumab. The resubmission stated that "[t]hese patients will be included in the current switch, discontinuation and active disease populations. These patients are not included separately in this analysis." The ESC and the PBAC considered that the grandfather restriction should be for subsequent-line usage only.

Financial Management – Risk Sharing Arrangements

6.34 No risk sharing arrangement (RSA) was detailed in the resubmission. The Sponsor did not acknowledge the RSA in place for ranibizumab and aflibercept in CNV due to AMD, or propose inclusion of brolucizumab in this RSA.

6.35 The resubmission stated that if the PBAC feels that the degree of uncertainty in the estimates warrants a RSA, the Sponsor will discuss this with the Department of Health once other aspects of the submission (with focus on the wording of the restriction and the size of the eligible population) have been agreed on.

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 brolucizumab for the treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD) in patients who have persistent disease despite prior anti-VEGF treatment. The PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of brolucizumab would be acceptable at a price lower than the currently PBS-listed anti-VEGF treatments.

7.2 The PBAC acknowledged that a second- or subsequent-line treatment option of brolucizumab in CNV due to AMD would be useful for some patients who have ongoing exudation/fluid despite prior anti-VEGF treatment.

7.3 The PBAC accepted the proposed dose equivalence of brolucizumab 6 mg, aflibercept 2 mg and ranibizumab 0.5 mg, in line with previous advice from the ESC and the PBAC (Brolucizumab PSD November 2019, paragraph 7.7). The PBAC noted the Sponsor offered a 5% price reduction for brolucizumab, when compared to the currently listed anti-VEGF treatments to account for differences in its safety, which could be calculated based on this dosing.

7.4 The restriction for brolucizumab recommended by the PBAC aligns with the current PBS listings for ranibizumab and aflibercept for initial and continuing treatment phases, with the exception of the requirement for initial treatment for patients to have persistent macular exudation, as determined clinically and/or on OCT or FA, despite at least 6 months of treatment with VEGF inhibitors. The PBAC noted that use of brolucizumab following both aflibercept and ranibizumab (i.e. third-line use) has not been excluded in the requested listing, and considered that second- or third-line use of brolucizumab would be reasonable.

7.5 The PBAC noted that switching between VEGF inhibitors is already occurring, and indicated that there may be flow-on changes required to the restrictions for ranibizumab and aflibercept to reflect this.

7.6 The requested restriction did not require that grandfathered patients must have previously received aflibercept and/or ranibizumab. The PBAC considered it would be

appropriate for grandfathered patients to be eligible to transition to PBS-subsidised treatment only if they are receiving brolucizumab as a second- or subsequent line treatment, and this should be reflected in the grandfather restriction.

7.7 The PBAC accepted aflibercept as the main comparator and ranibizumab as a secondary comparator in the second-line setting. The PBAC noted that switching between anti-VEGF treatments for inadequate- or non-response is common and well established.

7.8 The clinical evidence presented in the resubmission comprised the direct comparison between brolucizumab and aflibercept (HAWK and HARRIER trials) that have previously been considered by the PBAC, three single arm studies of patients switching to brolucizumab for second-line treatment, and multiple other data sources including case series and observational data. The PBAC considered the HAWK and HARRIER trials to be the key comparative evidence, despite these trials being conducted exclusively in a treatment naïve population, while the requested listing is for patients who have previously received at least 6 months of treatment with anti-VEGF treatments.

7.9 The resubmission presented secondary efficacy endpoints of anatomic criteria for brolucizumab versus aflibercept and claimed superiority in terms of efficacy. The PBAC considered this claim was not supported due to the uncertainty in translating these surrogate measures to patient-relevant clinical outcomes; however, it acknowledged that the Sponsor's arguments were biologically plausible and considered the anatomic data to be supportive of a non-inferiority claim for second-line use.

7.10 The PBAC reiterated its previous finding that it "was satisfied that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept, based on the two key trials (HAWK and HARRIER)" (Brolucizumab PSD November 2019, paragraph 7.3). The PBAC recalled that in both the HAWK and HARRIER trials, brolucizumab met the primary endpoint of non-inferiority in change in BCVA from baseline to Week 48 compared with aflibercept. The PBAC considered that non-inferiority of brolucizumab was reasonable based on extrapolation of first-line clinical data to the second- or subsequent-line setting. The PBAC considered that while the single arm switch studies were of low quality, they were not unsupportive of using brolucizumab second-line.

7.11 The PBAC considered that the issues of comparative safety identified in each of the previous brolucizumab submissions remain pertinent as the resubmission presented aflibercept as the main comparator. The PBAC reiterated its previous view that significantly higher rates of ocular serious adverse events were associated with brolucizumab compared to aflibercept (Brolucizumab PSD November 2019, paragraph 7.1). However, it acknowledged that the risk of RV/RVO is small and manageable if brolucizumab is restricted to a second-line setting.

7.12 The PBAC considered brolucizumab would be cost effective at the price proposed in the resubmission and if restricted to the second line treatment setting.

7.13 The PBAC noted the resubmission assumed there would be a cost associated with

loading doses of brolucizumab that patients maintained on aflibercept or ranibizumab would not incur and this resulted in an incremental cost to the PBS in the first few years of listing. The PBAC considered patients maintained on aflibercept or ranibizumab who are experiencing persistent disease are likely to be on 4 weekly injections and therefore loading doses of brolucizumab were unlikely to be an incremental cost to the PBS.

7.14 The PBAC considered that, overall, listing brolucizumab in the second- and subsequent-line treatment setting was likely to be cost neutral to Government as it was mainly expected to substitute for aflibercept and ranibizumab. The PBAC therefore advised that it would be appropriate for brolucizumab to join the Deed arrangements in place for ranibizumab and aflibercept in CNV due to AMD with no increase in expenditure caps to ensure the listing resulted in no additional cost.

7.15 The PBAC advised that brolucizumab is not suitable for prescribing by nurse practitioners.

7.16 The PBAC considered that the Early Supply Rule should not apply to brolucizumab.

7.17 The PBAC recommended that brolucizumab should not be treated as interchangeable with any other drugs.

7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because brolucizumab 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.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial treatment of subfoveal CNV

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats	Proprietary name and manufacturer
BROLUCIZUMAB 19.8 mg/0.165 mL injection, 0.165 mL syringe	NEW	1	1	2	Beovu Novartis Australia Pty Ltd

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing ☐Authority Required – Streamlined
	Indication: Subfoveal choroidal neovascularisation (CNV)
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD)
	AND
	Clinical criteria:
	Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of PBS-subsidised treatment with: 1. Aflibercept and/or 2. Ranibizumab
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Patient must not have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Prescribing Instructions: Authority approval for initial treatment of each eye must be sought.
	Prescribing Instructions: The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; and b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Services Australia 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 Services Australia website at 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

	Administrative Advice: No increase in the maximum number of repeats may be authorised
	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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*
	Administrative Advice: Special Pricing Arrangements apply

Continuing treatment of subfoveal CNV

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats	Proprietary name and manufacturer
BROLUCIZUMAB 19.8 mg/0.165 mL injection, 0.165 mL syringe	NEW	1	1	2	Beovu Novartis Australia Pty Ltd

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Authority Required – Streamlined
	Indication: Subfoveal choroidal neovascularisation (CNV)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD)
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have previously been granted an authority prescription for the same eye
	AND
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*
	Administrative Advice: Special Pricing Arrangements apply

Grandfather clause for treatment of subfoveal CNV

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats	Proprietary name and manufacturer
BROLUCIZUMAB 19.8 mg/0.165 mL injection, 0.165 mL syringe	NEW	1	1	2	Beovu Novartis Australia Pty Ltd

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing ☒~~Authority Required – Telephone/Electronic/Emergency~~ ☐Authority Required – Streamlined
	Indication: Subfoveal choroidal neovascularisation (CNV)
	Treatment Phase: Grandfather
	Clinical criteria:
	The condition must be due to age-related macular degeneration (AMD)
	AND
	Clinical criteria:
	The condition must be diagnosed by optical coherence tomography; or
	The condition must be diagnosed by fluorescein angiography
	AND
	Clinical criteria:
	Patient must have persistent macular exudation, as determined clinically and/or by optical coherence tomography or fluorescein angiography, despite at least 6 months of PBS-subsidised treatment with: 1. Aflibercept and/or 2. Ranibizumab.
	AND
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only per eye.
	Prescribing Instructions: The first authority application for each eye must be made in writing. A written application must include: a) a completed authority prescription form; b) a completed Subfoveal Choroidal Neovascularisation (CNV) - PBS Supporting Information Form; and c) a copy of the optical coherence tomography or fluorescein angiogram report.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Services Australia 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 Services Australia website at 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
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	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: No increase in the maximum quantity or number of units may be authorised *for applications treating one eye*
	Administrative Advice: Special Pricing Arrangements apply
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

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

Novartis welcomes the decision by the PBAC to recommend the PBS listing of brolucizumab (Beovu) and are committed to make this treatment available to Australian patients with age related macular degeneration.