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

1 Purpose of Application

1.1 The minor resubmission requested an Authority Required listing for brolucizumab for treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD). Listing was requested on the basis of a cost-minimisation analysis (CMA) versus aflibercept as the main comparator and ranibizumab as a secondary comparator.

1.2 The minor resubmission sought to address the outstanding clinical areas of concern relating to the previous submissions of brolucizumab considered in November 2019 (major) and March 2020 (minor). The purpose of this resubmission was to address the claim of non-inferior safety and difference in safety profile.

2 Background

Registration status

2.1 The November 2019 submission was made under TGA/PBAC Parallel Process. The Delegate's Overview was provided prior to the PBAC meeting and stated there is no reason that the application for brolucizumab should not be approved for the treatment of neovascular (wet) AMD. However, the Delegate noted the higher rate of ocular adverse events (AEs) associated with brolucizumab and requested Advisory Committee on Medicines (ACM) advice on a number of safety issues.

2.2 The ratified resolution from the ACM meeting on 6 December 2019 was provided with the March 2020 minor resubmission. The ACM provided advice on the safety issues raised by the Delegate and considered brolucizumab had an overall positive benefit-risk profile. Brolucizumab was approved by the TGA for the treatment of neovascular (wet) AMD and listed on the Australian Register of Therapeutic Goods (ARTG) on 16 January 2020.

2.3 The Sponsor lodged an update to the brolucizumab Product Information (PI), Consumer Medicines Information (CMI), and Risk Management Plan (RMP) with the TGA in May 2020 to reflect new safety information as documented in the report "Medical Assessment of Post-Marketing Case Reports" (paragraph 5.7). The TGA completed their review of this information in May 2020 and recommended changes

to the PI, CMI and RMP to reflect the emergent post-market safety signal for retinal vasculitis and/or retinal vascular occlusion with or without intraocular inflammation.

2.4 The Sponsor stated in their pre-PBAC response that the TGA have concluded the review of the safety assessment report and approved the related change to the approved PI, as well as the risk management activities proposed. The Sponsor indicated that the HCP targeted educational campaign would begin in early July 2020 with the supply of brolucizumab through a named patient program commencing in Australia on 6 July 2020. The Sponsor stated in their pre-PBAC response that there does not appear to be any obstacle to a patient enrolled in a named patient programme (and receiving non-PBS brolucizumab) being able to access PBS stock under the proposed restrictions.

Previous PBAC consideration

2.5 Brolucizumab was previously considered by the PBAC for this indication in November 2019 and it was not recommended. The PBAC considered that the claim of non-inferior effectiveness of brolucizumab compared with aflibercept was reasonable based on two key trials (HAWK and HARRIER) (paragraph 7.3, brolucizumab public summary document [PSD], November 2019). The PBAC considered the claim of non-inferior safety to be uncertain.

2.6 The March 2020 minor resubmission addressed two issues associated with the CMA of brolucizumab against aflibercept/ranibizumab. The minor resubmission employed a 1:1 dose relativity in the CMA, consistent with the previous PBAC advice that there were no clinical reasons for dosing frequencies amongst brolucizumab and anti-vascular endothelial growth factors (anti-VEGFs) to be different to each other (paragraph 6.5, brolucizumab PSD, March 2020). The Sponsor also used the ranibizumab price based on ranibizumab being the least costly comparator consistent with previous PBAC advice (paragraph 6.6, brolucizumab PSD, March 2020). However, the PBAC considered that the CMA was not adequately supported as non-inferior safety of brolucizumab had not been established.

2.7 The March 2020 minor resubmission also sought to address outstanding safety concerns with brolucizumab by providing the ratified resolution of the ACM Meeting (paragraph 2.2). The Sponsor's pre-PBAC response stated that on 23 February 2020, the American Society of Retinal Specialists (ASRS) shared with its membership that it had received some anecdotal reports of retinal artery occlusion and intraocular inflammation since brolucizumab approval in the United States. The PBAC noted these reports and considered further clarity was required regarding these safety issues with brolucizumab.

2.8 Table 1 provides a summary of the key issues identified by the PBAC at the March 2020 meeting and the manner in which the July 2020 minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in March 2020 and how they were addressed in the July 2020 minor resubmission

Issue identified by PBAC in March 2020 Public Summary Document	How issue was addressed in July 2020 resubmission
[paragraph 6.3] The PBAC noted the relative risk for ocular SAEs for brolucizumab compared to aflibercept was 2.27 (95% CI: 1.12, 4.58) and the relative risk for specific ocular AEs was >1 for most outcomes (favouring aflibercept) with wide confidence intervals (Table 5, brolucizumab PSD, November 2019). The PBAC noted the ACM findings regarding the safety of brolucizumab but considered the claim of non-inferior comparative safety versus aflibercept remained uncertain. The PBAC further noted the anecdotal reports from the ASRS … and considered this increased the uncertainty of the non-inferior safety claim. [paragraph 6.4] The PBAC noted there were two safe and efficacious treatment options available for patients and considered the need for additional treatment options was low, particularly one with uncertain comparative safety. [paragraph 6.8] The PBAC considered any future submission could be a minor resubmission and should address the uncertain claim of non-inferior safety.	The Sponsor has provided: • Brolucizumab medical line listings (64 cases) • Brolucizumab medical CIOMS forms (64 cases) • Brolucizumab medical assessment report • Communication between Novartis and the TGA • Cost of treating inflammation in HAWK and HARRIER trials (unchanged from Nov 2019 submission).

2.9 ACM = Advisory Committee on Medicines; AE = adverse event; CIOMS = Council for International Organizations of Medical Sciences; PSD = Public Summary Document; SAE = serious adverse event.

2.10 The cost of treating inflammation in the HAWK and HARRIER trials (calculated as $[redacted] in the brolucizumab arm and $[redacted] in the aflibercept arm, an incremental cost of approximately $[redacted] per patient per year) was based on the use of topical or systemic corticosteroids, topical antibiotics/anti-infectives or antivirals, for treatment-related ocular AEs. The Sponsor stated in their November 2019 submission that the significantly higher rate of ocular adverse events used to calculate this cost was likely driven by rates of uveitis and iritis reported in the HAWK trial. In contrast, the emergent post-market safety signal for retinal vasculitis and/or retinal vascular occlusion with or without intraocular inflammation represents a subset of serious AEs that can lead to central or branch retinal artery occlusion (CRAO/BRAO). CRAO can result in severe vision loss, for which the ASRS states there is no clinically proven treatment.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 A restriction was proposed by the Sponsor for initial treatment, continuing treatment and grandfathered patients with the March 2020 minor resubmission, as presented in the PBAC PSD from the March 2020 meeting (paragraph 3.1). The Sponsor confirmed the requested restriction remained unchanged in their pre-PBAC response for the July 2020 minor resubmission. The restriction has undergone further minor review and is summarised below; suggestions and additions proposed by the Secretariat to the

requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
BROLUCIZUMAB brolucizumab 19.8 mg in 0.165 mL syringe	NEW	1	1	2	Effective: $[redacted] Published: $1042.60	Beovu

Initial treatment of subfoveal CNV

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ☒Authority Required – In Writing (follow up after initial facsimile application) ☒Authority Required – Telephone/Online
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:
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 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 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: *Where both eyes are being treated simultaneously, a quantity of 2 ~~vials~~ pre-filled syringes can be requested on the same authority prescription form.*
Prescribing Instructions:

A Grandfathered patient who has previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date] must have met all the initial criteria under this restriction prior to PBS-subsidised initial treatment. A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. This Grandfather patient access will cease from [insert a date which is 12 months from listing date here]
Administrative Advice: The first authority application may be faxed to the ~~Department of Human~~ Services *Australia* on 1300 093 177 ~~(hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)~~. ~~The Department~~ *Services Australia* will then contact the prescriber by telephone.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the ~~Department of Human~~ 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 ~~Department of Human~~ Services *Australia* website at www.~~human~~services*australia*.gov.au Applications for authority to prescribe should be ~~forwarded to:~~ *submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* ~~Department of Human~~ 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: *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

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ☒Authority Required – Telephone/Electronic/Emergency
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 in consultation with an ophthalmologist
Prescribing Instructions:

Where both eyes are being treated simultaneously, a quantity of 2 ~~vials~~ pre-filled syringes can be requested on the same authority prescription form
Administrative Advice: Authority approvals will be administered by the Complex Drugs Unit of ~~the Department of Human~~ Services *Australia*
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)~~
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: *No increase in the maximum quantity or number of units may be authorised for applications treating one eye*
Administrative Advice: Special Pricing Arrangements apply

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The November 2019 submission nominated aflibercept as the main comparator and ranibizumab as a secondary comparator (paragraph 7.2, brolucizumab PSD, November 2019). 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.

4.2 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 previously 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 (paragraph 5.3, brolucizumab PSD, November 2019).

4.3 The March 2020 and July 2020 minor resubmissions did not update the proposed comparator.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from health care professionals (9) via the Consumer Comments facility on the PBS website. The comments described a range of

benefits of treatment with brolucizumab, including treatment for patients who have become unresponsive to the currently listed anti-VEGF treatments and extension of treatment intervals to 3 months in patients who are currently having monthly injections. The consumer comments indicated ocular adverse events are considered rare and manageable.

Clinical trials

5.3 The November 2019 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)),[1] and one supplementary randomised trial (OSPREY, n=89), in patients with neovascular AMD. No new clinical trial evidence was presented in the March 2020 and July 2020 minor resubmissions. Details of the trials presented in the November 2019 submission can be found in Table 2, brolucizumab PSD.

5.4 In the HAWK and HARRIER trials, patients in both the brolucizumab and the aflibercept treatment arms received 3 loading doses administered at monthly intervals, followed by maintenance regimens:

- Brolucizumab 6 mg every 12 or 8 weeks (q12/8w), depending on whether there was evidence of disease activity; subjects identified with a q8w need were switched to a q8w treatment interval for the remainder of the study.
- Aflibercept 2 mg every 8 weeks (q8w).

5.5 The administration of aflibercept every 8 weeks following the initial 3 loading doses 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 PBAC maintained its previous view that the mean number of injections per patient in the trials is unlikely to be representative of aflibercept utilisation in Australia.

Comparative effectiveness

5.6 The PBAC previously considered that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept, based on the two key trials (HAWK and HARRIER) (paragraph 7.3, brolucizumab PSD, November 2019).

Comparative harms

5.7 The PBAC previously considered that the overall ocular serious adverse event (SAE) rate with brolucizumab (3.4%) was significantly different to aflibercept (1.5%) and the

[1] Number of patients in the relevant treatment arms (full analysis set)

claim of non-inferiority in terms of safety was uncertain (paragraph 7.3, brolucizumab PSD, November 2019). 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. The PBAC maintained this view in March 2020, noting that the relative risk for ocular SAEs for brolucizumab compared to aflibercept was 2.27 (95% CI: 1.12, 4.58) and the relative risk for specific ocular AEs was >1 for most outcomes (favouring aflibercept) with wide confidence intervals (paragraph 6.3, brolucizumab PSD, March 2020).

5.8 Following the TGA Delegate's request for ACM advice on a number of safety issues associated with brolucizumab, the Ratified Resolution from the TGA ACM meeting on 6 Dec 2019 provided additional information regarding the safety profile of brolucizumab (paragraph 5.6, brolucizumab PSD, March 2020). The ACM noted that most treatment emergent adverse events were minor and the variation in their incidence was likely determined by chance, that most cases of intraocular inflammation are transient and treatable with topical or systemic corticosteroid therapy, and that clinically significant inflammation or uveitis are rare. The Sponsor stated in the March 2020 resubmission that the findings of the TGA ACM support the claim of non-inferiority.

5.9 The PBAC noted the ACM findings regarding the safety of brolucizumab but considered the claim of non-inferior comparative safety versus aflibercept remained uncertain. The PBAC further noted the anecdotal reports from the ASRS and considered this increased the uncertainty of the non-inferior safety claim (paragraph 6.3, brolucizumab PSD, March 2020).

5.10 In light of the anecdotal reports from the ASRS of retinal artery occlusion and intraocular inflammation, the July 2020 minor resubmission provided a report from the Global Novartis Ophthalmology team titled "Medical assessment of post-marketing case reports". The report included the following information:

- All post-marketing case reports in the Novartis Safety Database relating to brolucizumab were reviewed by a Safety Review Committee (SRC), with cases of interest ([redacted] cases) having preferred terms of retinal artery occlusion ([redacted] cases), retinal vasculitis ([redacted] cases), and severe vision loss ([redacted] cases). The SRC determined that the cases could best be described using preferred terms retinal vasculitis and retinal vascular occlusion, with or without an intraocular inflammation.
- Case reports across all indications were reported to the FDA for aflibercept: 98 cases of retinal artery/vein occlusion and 5 cases of retinal vasculitis.
- Case reports across all indications were reported to the FDA for ranibizumab: [redacted] cases of retinal artery/vein occlusion and [redacted] cases of retinal vasculitis. The ranibizumab Periodic Safety Update Report (PSUR) was reviewed with a conclusion that retinal artery occlusion is not considered an AE with

ranibizumab, and that no change to the ranibizumab product label or RMP was warranted. The cumulative exposure for ranibizumab is 6.5 million patient treatment years.

5.11 The report from the Global Novartis Ophthalmology team contained the following discussion/conclusions:

> "The internal and SRC review of post-marketing case reports detected an emerging new safety signal of retinal vasculitis and/or retinal vascular occlusion with or without presence of intraocular inflammation that may result in severe vision loss associated with Beovu treatment. … Additionally, these events in the Phase III clinical studies were generally less severe than the post-marketing cases."
>
> "The Core Data Sheet will be amended to add retinal vasculitis and/or retinal vascular occlusion with or without presence of intraocular inflammation under warnings and precaution, and to add retinal vasculitis and retinal vascular occlusion as new adverse drug reactions."

The PIs for aflibercept and ranibizumab do not contain analogous warnings and precautions.

5.12 The Sponsor stated in the July 2020 resubmission that "The acceptable updates to the brolucizumab PI, CMI and RMP by the TGA based on the review of the reports from the ASRS should provide the PBAC with sufficient assurance that the safety events will be adequately managed in Australia, and that the benefit-risk for brolucizumab is favourable". The TGA indicated in May 2020 that updates to the PI and CMI should reflect the emergent post-market safety signal for retinal vasculitis and/or retinal vascular occlusion, which in some cases could result in permanent vision loss and blindness. The PI was finalised by the TGA with revised safety information in June 2020.

5.13 Ranibizumab and brolucizumab are contraindicated in patients with active intraocular inflammation. Aflibercept is contraindicated in patients with active severe intraocular inflammation. The Sponsor stated in the July 2020 resubmission that physicians should follow the guidance in the prescribing information that patients with active inflammation should not be injected with brolucizumab. The discussion in the Global Novartis Ophthalmology report referred to a potential causal association between brolucizumab and retinal vasculitis and/or retinal vascular occlusion with or without presence of intraocular inflammation, and stated that the events reviewed occurred early after starting treatment.

Clinical claim

5.14 The PBAC previously considered that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept, and that the claim of non-inferiority in terms of safety was uncertain (paragraph 7.3, brolucizumab PSD, November 2019).

5.15 Following the resolution from the TGA ACM meeting on 6 December 2019, the Sponsor stated that the findings of the ACM support the claim of non-inferior safety, and that their changes to the brolucizumab PI, CMI and RMP should give assurance to the PBAC that safety events will be adequately managed (paragraph 5.8). Following the review of the emergent post-market safety signal for retinal vasculitis and/or retinal vascular occlusion with or without intraocular inflammation in May 2020, the PI has now been updated and finalised by the TGA in June 2020.

5.16 The November 2019 submission claimed that brolucizumab would provide the benefit of less frequent dosing (every 2 to 3 months) compared with currently available anti-VEGFs (every 2 months), while maintaining the same efficacy. The PBAC considered this to be inappropriate and noted that in Australian practice, the 'treat and extend' regimen is expected and should apply to all anti-VEGF injections and that there are no clinical reasons for dosing frequencies amongst them to be different to each other (paragraph 7.4 and 7.5, brolucizumab PSD, November 2019 PBAC meeting). While the Sponsor employed a 1:1 dosing relativity for the CMA in the March 2020 resubmission (paragraph 5.15), it argued in the July 2020 resubmission that "Clinicians and patients with wAMD should be offered access to brolucizumab on the PBS given the particularly high burden for some patients who require ongoing monthly injections. Brolucizumab offers the opportunity to reduce this burden for patients".

5.17 The Sponsor reiterated in their pre-PBAC response for the July 2020 minor resubmission that brolucizumab has demonstrated greater effective control of anatomical disease activity compared with aflibercept in the HAWK and HARRIER trials. The Sponsor stated that over 50% of subjects were able to be maintained on a regimen of brolucizumab q12w up to Week 44, whilst achieving non-inferiority in best corrected visual acuity (BCVA) to aflibercept with a q8w treatment interval.

5.18 There is no clinical evidence that brolucizumab will permit fewer injections, and a 'treat and extend' regimen is supported in the PIs for all three agents. The submission did not present any data to support the use of brolucizumab in a subset of patients who may require monthly injections. The administration of aflibercept every 8 weeks in the HAWK and HARRIER trials was not consistent with the treatment strategy most commonly employed in Australian clinical practice (T&E regimen), and the PBAC maintained its previous view that the mean number of injections per patient is unlikely to be representative of aflibercept utilisation in Australia (paragraph 5.5).

5.19 The PBAC reiterated that the claim brolucizumab was of non-inferior comparative effectiveness versus aflibercept was reasonable. The PBAC considered the claim of non-inferior comparative safety remained uncertain.

Economic analysis

5.20 The July 2020 minor resubmission appropriately assumed a 1:1 substitution of brolucizumab for aflibercept using an identical number of injections ([redacted]) (paragraph 2.6) and assumed the ranibizumab price in the CMA.

5.21 With 1:1 substitution at the ranibizumab price, brolucizumab pricing would be identical to that of ranibizumab at published and effective levels. The published and effective ex-manufacturer prices associated with ranibizumab are $932.40 and $[redacted], respectively.[2] The results of the CMA based on the effective ex-manufacturer prices for ranibizumab and brolucizumab can be found in Table 3, brolucizumab PSD, March 2020. In the pre-PBAC response to the July 2020 minor resubmission, the Sponsor proposed a [redacted]% price reduction relative to the lowest cost comparator, ranibizumab, to account for the uncertainty associated with managing the incremental cost of treating SAEs associated with brolucizumab (paragraph 5.22). Thus, the new effective AEMP proposed for brolucizumab is $[redacted]/syringe and new effective dispensed price for maximum quantity [DPMQ] proposed is $[redacted]/syringe.

5.22 The incremental cost of treating SAEs in brolucizumab patients was estimated by the Sponsor to be $[redacted] per patient per year (paragraph 2.9). These events were described by the ACM as being treatable with topical or systemic therapy (corticosteroids) and thus transient, and that clinically significant inflammation is rare (paragraph 5.8). The Sponsor did not include this additional cost in the cost-minimised price of brolucizumab. These treatable SAEs are distinct from the emergent safety signal for retinal vasculitis and/or retinal vascular occlusion, of which a complication is CRAO/BRAO, potentially leading to vision loss, for which there is no clinically proven treatment. The pre-PBAC response stated that retinal vasculitis and/or retinal vascular occlusion are included in the spectrum of intraocular inflammatory events, and the costs are captured as part of the costing data of the trials. However, the Sponsor acknowledged that there may be uncertain costs in managing these events in clinical practice relative to the costs calculated from the trial evidence, and thus proposed the [redacted]% price reduction to brolucizumab to ensure that there is no added cost to the government (paragraph 5.21).

5.23 The March 2020 resubmission stated consideration under Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth for the comparator price prior to the F1 anniversary price reductions would be discussed with the Department of Health as appropriate once a positive recommendation for brolucizumab has been received (paragraph 5.19, brolucizumab PSD, March 2020). The Sponsor clarified in the pre-PBAC response that consideration under Clause 5.7 would not be pursued.

Drug cost/patient/year: $[redacted] (based on effective price)

5.24 The estimated brolucizumab cost/patient/year at the price proposed in the July 2020 resubmission would be $[redacted], based on [redacted] injections per year and a dispensed price for maximum quantity (DPMQ) of $[redacted] (effective price).

[2] Since ranibizumab is provided by the same Sponsor, the effective price is known by the Sponsor.

5.25 The estimated brolucizumab cost/patient/year incorporating the [redacted]% price reduction relative to the lowest cost comparator, ranibizumab, as per the pre-PBAC response to the July 2020 minor resubmission (paragraph 5.21), would be $[redacted], based on 6.03 injections per year and a DPMQ of $[redacted] (effective price).

Estimated PBS usage & financial implications

5.26 The July 2020 resubmission estimated a net saving to the PBS/RPBS of less the $10 million in Year 6 of listing, using effective prices, with a total net saving to the PBS/RPBS of $20 - $30 million over the first 6 years of listing (unchanged from March 2020 resubmission). The cost savings are summarised in Table 2, as well as the expected prescription numbers.

Table 2: Estimated use and financial implications of brolucizumab to the PBS/RPBS

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use							
Scripts dispensed[a]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brolucizumab scripts		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of brolucizumab (net cost to PBS/RPBS[b])							
Brolucizumab		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated treatment replaced							
Aflibercept	2168D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	10138N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	1382R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of treatment replaced (net cost to PBS/RPBS[b])							
Aflibercept	2168D	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Ranibizumab	10138N	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Ranibizumab	1382R	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications							
MBS net cost		$0	$0	$0	$0	$0	$0
Net cost to PBS/RPBS/MBS (March 2020 resubmission)		$-[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Abbreviations: AMD = age-related macular degeneration; CNV = choroidal neovascularisation; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Source: Section 4 Workbook_'PBS-RPBS overview tab'.
[a] Total anti-VEGF scripts for CNV due to AMD.
[b] Costs represent DPMQ minus copayment at the effective price and do not incorporate the [redacted]% price reduction proposed in the pre-PBAC response for the July 2020 resubmission.

The redacted table shows that at Year 6, the estimated number of brolucizumab scripts dispensed was over 200,000.

5.27 As a minor submission, the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangements

5.28 The March 2020 resubmission noted that ranibizumab and aflibercept currently have risk sharing arrangements in place covering PBS expenditure in relation to the treatment of neovascular AMD. The March 2020 resubmission stated that the degree to which these arrangements would, or would not, apply to brolucizumab is not known at this stage. However, the sponsor expects this to be central part of post-PBAC negotiations once a positive recommendation is received. The July 2020 resubmission did not alter this position.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC outcome

6.1 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 considered that the claim of non-inferior safety was not adequately demonstrated and that brolucizumab is likely inferior to aflibercept in terms of comparative safety. The PBAC recalled it had previously considered brolucizumab was non-inferior in terms of comparative efficacy but would not provide the benefit of less frequent dosing compared with currently available anti-VEGFs as claimed by the sponsor.

6.2 The PBAC noted the consumer comments stating that a treatment option that could extend treatment intervals to 3 months would be beneficial, and that safety concerns regarding rare cases of intraocular inflammation and vasculitis should not preclude its use. The PBAC also noted the comments 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).

6.3 The PBAC previously considered that clinical data indicated a significant difference between brolucizumab and aflibercept in serious adverse events (SAEs). The PBAC noted the relative risk for ocular SAEs for brolucizumab compared to aflibercept was 2.27 (95% CI: 1.12, 4.58) and the relative risk for specific ocular AEs was >1 for most outcomes (favouring aflibercept) with wide confidence intervals (Table 5, brolucizumab PSD, November 2019). The PBAC noted that the Global Novartis Ophthalmology report identified an emerging new safety signal of retinal vasculitis and/or retinal vascular occlusion with or without presence of intraocular inflammation that may result in severe vision loss associated with brolucizumab. The PBAC noted the TGA have approved changes to the brolucizumab PI to reflect this emerging safety signal.

6.4 Based on the clinical trial evidence of a significant difference in SAEs between brolucizumab and aflibercept, and changes made to the approved PI to reflect an

emerging safety signal, the PBAC concluded that brolucizumab is likely inferior to aflibercept in terms of comparative safety.

6.5 While the PBAC previously considered the claim of non-inferior effectiveness of brolucizumab compared with aflibercept was reasonable, it 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, based on the HAWK and HARRIER studies (paragraph 7.4, brolucizumab PSD, November 2019).

6.6 The PBAC acknowledged that the frequency of SAEs (retinal vasculitis and/or retinal vascular occlusion with or without presence of intraocular inflammation) that may result in severe vision loss, as documented by the ASRS, was rare. However, the PBAC maintained its view that there were two safe and efficacious treatment options available for patients and considered the need for additional treatments was low, particularly one with likely inferior safety. The PBAC considered that unnecessary risk may be associated with brolucizumab with no additional benefit compared to the treatment options already available.

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

Outcome:
Rejected

7 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.

8 Sponsor's Comment

Novartis disagrees with the decision of the PBAC not to recommend the listing of Beovu® on the PBS for the treatment of wet AMD. Beovu® has now been approved in more than 30 countries, including all major markets, and Novartis and Australian clinicians believe that Beovu® represents an important treatment option for patients with wet AMD, with an overall favourable benefit-risk profile. Novartis will continue to work collaboratively with the PBAC, the Department of Health and the Federal Government to help ensure that Australians with wet AMD receive access to Beovu® through the PBS at the earliest opportunity.