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

1 Purpose of Application

1.1 The 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 versus aflibercept as the main comparator and ranibizumab as a secondary comparator, with ranibizumab being the least costly comparator.

1.2 The minor resubmission sought to address the outstanding clinical, economic and financial areas of concern relating to the previous submission of brolucizumab, which was considered at the November 2019 PBAC meeting.

2 Background

Registration status

2.1 The November 2019 submission was made under TGA/PBAC Parallel Process and was not TGA registered at the time of PBAC consideration. The second round Clinical Evaluation Report and TGA Delegate's Overview were provided prior to the PBAC meeting. The Delegate's Overview stated 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 resolution from the ACM meeting on 6 December 2019 was provided with the minor resubmission. The ACM provided advice on the safety issues raised by the Delegate and considered brolucizumab had an overall positive benefit-risk profile. The Sponsor stated that the findings of the ACM support the claim of non-inferiority.

2.3 Following receipt of the minor resubmission, brolucizumab has been approved by the TGA for the treatment of neovascular (wet) AMD, and was listed on the Australian Register of Therapeutic Goods (ARTG) on 16 January 2020.

Previous PBAC consideration

2.4 Brolucizumab was previously considered by the PBAC for this indication in November 2019. It was not recommended.

2.5 Table 1 provides a summary of the key issues identified by the PBAC at the November 2019 meeting and the manner in which the minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in November 2019 and how they were addressed in the minor resubmission

Issue identified by PBAC in November 2019 Public Summary Document	How issue was addressed in March 2020 resubmission
[paragraph 7.2] The submission nominated aflibercept as the main comparator as it has a higher market share, and ranibizumab as a secondary comparator. The PBAC noted that ranibizumab had become the least costly comparator since the F1 anniversary price reduction applied to ranibizumab (10%) and aflibercept (5%) on 1 April 2018. The PBAC noted that no data were provided demonstrating brolucizumab provides a significant improvement in efficacy or reduction of toxicity over the alternative therapies (aflibercept and ranibizumab) (paragraph 5.3). The PBAC advised that the drug cost used for the CMA should be the effective ranibizumab price rather than the weighted price of aflibercept and ranibizumab, as ranibizumab is the least costly anti-VEGF agent.	The Sponsor has accepted the ranibizumab price for brolucizumab in the minor resubmission.
[paragraph 7.3] …the PBAC considered that the overall ocular SAE rate with brolucizumab (3.4%) was significantly different to aflibercept (1.5%) and the claim of non-inferiority in terms of safety was uncertain. The ocular SAEs that occurred more frequently with brolucizumab included uveitis, vitreous floater and retinal pigment epithelial tear. The PBAC considered that the safety profile of brolucizumab is uncertain compared to its comparators, and there are potential associated cost implications. [paragraph 7.7] The PBAC considered that any future submission should address the uncertain claim of non-inferior safety and difference in safety profile through a price reduction against the lowest cost alternative …	The Sponsor has provided the ratified resolution of the ACM Meeting that occurred on 6 December 2019. The ACM addressed the safety questions raised by the TGA Delegate and the Sponsor claims this supports non-inferiority.
[paragraph 7.4] The PBAC did not consider brolucizumab would provide the benefit of less frequent dosing compared with currently available anti-VEGFs (as claimed in the submission), while maintaining the same efficacy, because the dosing regimens for brolucizumab and aflibercept in both HAWK and HARRIER were not as flexible as those specified in the respective PIs. [paragraph 7.5] …The PBAC considered that the CMA should assume an identical number of injections (6.03) for aflibercept/ranibizumab and brolucizumab, as it is highly uncertain that there will be any difference in injection frequency between brolucizumab, aflibercept and ranibizumab in clinical practice.	The Sponsor has accepted that the CMA should assume an identical number of injections (6.03) for aflibercept / ranibizumab and brolucizumab.

ACM = Advisory Committee on Medicines; CMA = cost minimisation analysis; PI = Product Information; SAE = serious adverse event; VEGF = vascular endothelial growth factor.

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 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	Proprietary Name and Manufacturer	
BROLUCIZUMAB brolucizumab 19.8 mg in 0.165 mL syringe [new MPP]	NEW	1	1	2	Effective: $[redacted] Published: $[redacted]	Beovu® [new TPP]	Novartis Australia Pty Ltd

Initial treatment of subfoveal CNV

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:
The treatment must be the sole PBS-subsidised therapy for this condition
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 can be requested on the same authority prescription form.*
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: ☐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 in consultation with an ophthalmologist
Prescribing Instructions: *Where both eyes are being treated simultaneously, a quantity of 2 vials 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

Grandfather subfoveal CNV

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: Grandfathered treatment
Clinical criteria:
The condition must be due to age-related macular degeneration (AMD)
AND
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date]
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
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 can be requested on the same authority prescription form.*
Administrative advice:

Patients 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.
Administrative advice: *This grandfather restriction will cease to operate 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

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

4 Comparator

4.1 The November 2019 submission nominated aflibercept as the main comparator and ranibizumab as a secondary comparator (paragraph 5.1, brolucizumab Public Summary Document (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 comparators remained unchanged from the previous submission and the clinical claim continued to be based on a comparison with aflibercept. The cost-minimisation analysis (CMA) in the resubmission was updated to be against the least costly comparator (ranibizumab), rather than weighted between ranibizumab and aflibercept prices according to PBS volumes in 2018.

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 that no consumer comments were received for this item.

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 evidence was presented in the minor resubmission. Details of the trials presented in the November 2019 submission are provided in Table 2.

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

Table 2: Trials and associated reports presented in the resubmission

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

Source: Table 2, brolucizumab PSD, November 2019 PBAC meeting.

Comparative effectiveness

5.4 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

5.5 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 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.

5.6 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 became available. The ACM provided additional information regarding the safety profile of brolucizumab in the resolution, as follows:

- "The ACM noted that most treatment emergent adverse events were minor and the variation in their incidence was likely determined by chance."

- "The ACM advised that arteriothomboembolic events (ATE) are potentially related to VEGF inhibition. The ATE rate was 4.5% (33/730) in brolucizumab treated eyes and 4.7% (34/729) in aflibercept treated eyes. ATE are more common in patients with wet AMD than those without."
- "The ACM considered the rate of endophthalmitis to be very high in all treatment groups of both trials (0.6%, to 1.3%)." ….. "The ACM was of the view that the difference in endophthalmitis between brolucizumab and aflibercept appears to be due to chance alone, and has been noted in previous trials comparing aflibercept with ranibizumab and bevacizumab (CATT trial)."
- "….the ACM advised that in general, most cases of intraocular inflammation are treatable with topical or systemic therapy (corticosteroids) and thus transient, and that clinically significant inflammation is rare."
- "The ACM was of the view that this [uveitis] is likely the result of the drug rather than disease, but the causes of this are unclear. The ACM noted however that this uveitis is rarely clinically significant and that in practice, the same anti-VEGF therapy can result in reactions in the same patient on some occasions, but not others."

5.7 The PSD for the November 2019 submission stated that the PBAC considered that any future submission should address the uncertain claim of non-inferior safety and difference in safety profile through a price reduction against the lowest cost alternative (paragraph 7.7, brolucizumab PSD, November 2019). The Sponsor stated in the minor resubmission that the findings of the TGA ACM support the claim of non-inferiority because:

- potential bias in clinical trials captured higher rates of intraocular inflammation compared with clinical practice;
- most TEAEs were minor and any variation in incidence determined by chance;
- inflammation is treatable and transient and clinically insignificant;
- uveitis is rarely clinically significant with unknown cause;
- endophthalmitis occurs due to chance alone.

5.8 The pre-PBAC response stated that on 23 February 2020, the American Society of Retinal Specialists (ASRS) shared with its membership that it has received some anecdotal reports of retinal artery occlusion and intraocular inflammation since brolucizumab approval in the United States. The Sponsor commented that such events were observed in the clinical trials and their incidence are consistent with the TGA-approved Product Information. The Sponsor has informed the relevant section of the TGA as required by routine pharmacovigilance reporting. The PBAC noted these reports and considered further clarity was required regarding these safety issues with brolucizumab.

Clinical claim

5.9 The November 2019 submission described brolucizumab 6 mg as non-inferior in terms of effectiveness and equivalent in terms of safety compared with aflibercept 2 mg. The minor resubmission did not update the clinical claim.

5.10 The PBAC previously considered that brolucizumab was non-inferior in terms of comparative efficacy to aflibercept (paragraph 7.3, brolucizumab PSD, November 2019).

5.11 The PBAC previously considered the claim that brolucizumab was non-inferior in terms of comparative safety compared with aflibercept was uncertain (paragraph 7.3, brolucizumab PSD, November 2019). Following the resolution from the TGA ACM meeting on 6 December 2019, the Sponsor stated in the minor resubmission that the findings of the ACM supported the claim of non-inferior safety. However, the pre-PBAC response stated that the ASRS had received reports of safety issues with brolucizumab since its approval in the United States (paragraph 5.8).

5.12 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 (paragraphs 7.4 and 7.5, brolucizumab PSD, November 2019 PBAC meeting).

5.13 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

5.14 The November 2019 submission presented a CMA of brolucizumab to aflibercept based on direct randomised trials of HAWK and HARRIER. The equi-effective doses were estimated by the Sponsor as brolucizumab 6 mg [redacted] administrations per year and aflibercept 2 mg [redacted] administrations per year for the maintenance treatment phase. The ESC previously noted that the dosing regimens for both brolucizumab and aflibercept in the clinical trials were less flexible than that specified in the respective Product Information. Consequently, the ESC previously considered that the differential number of doses for brolucizumab and aflibercept/ranibizumab in the CMA may not be reflected in clinical practice (paragraph 6.27, Brolucizumab ESC advice, November 2019). The equi-effective doses were revised by the Sponsor in the previous Pre-PBAC response to an identical number of injections (6.03). The PBAC considered this to be appropriate (paragraph 7.5, brolucizumab PSD, November 2019).

5.15 The minor resubmission assumed a 1:1 substitution of brolucizumab for aflibercept using an identical number of injections (6.03), which is consistent with the view of the ESC and the PBAC.

5.16 The November 2019 submission proposed a brolucizumab price weighted according to the relative utilisation of aflibercept and ranibizumab in 2018. The PBAC considered this to be inappropriate, and indicated that the brolucizumab price used for the CMA should be the effective ranibizumab price, as it is the least costly anti-VEGF comparator (paragraphs 4.2 and 4.3).

5.17 The minor resubmission assumed the ranibizumab price in the CMA, which is consistent with the view of the ESC and the PBAC.

5.18 With 1:1 substitution at the ranibizumab price, a simple CMA can be performed based on equi-effective doses. Brolucizumab pricing will 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 are provided in Table 3.

Table 3: Results of the cost minimisation analysis

		Ranibizumab	Brolucizumab	Source/calculation
A	Ex-manufacturer price (effective)	$[redacted]	$[redacted]	Ranibizumab = ex-manufacturer price Brolucizumab = C / B
B	Injections	6.03	6.03	Pooled average doses between weeks 48 and 92 in the HAWK and HARRIER trials for aflibercept, adjusted to yearly
C	Drug Costs	$[redacted]	$[redacted]	Ranibizumab = A * B Brolucizumab = E – D
D	Administration Costs	$1,813.52	$1,813.52	Both arms = B * $300.75 (MBS Item 42740)
E	Total cost per year (ex-manufacturer)	$[redacted]	$[redacted]	Ranibizumab = C + D Brolucizumab = assumed equal to ranibizumab

5.19 The November 2019 major submission requested that the comparator price prior to the F1 anniversary price reductions apply to brolucizumab, according to Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth (the Strategic Agreement), until expiration of the agreement 30 June 2022. The PBAC noted in the PSD that application of the Strategic Agreement is not a matter for PBAC. The minor resubmission states that this scenario has not been modelled in the resubmission financial estimates, but will be discussed with the Department of Health as appropriate once a positive recommendation has been received.

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

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

5.20 The estimated brolucizumab cost/patient/year, as per the minor resubmission, would be $[redacted], based on 6.03 injections per year and a dispensed price for maximum quantity (DPMQ) of $[redacted] (effective price).

Estimated PBS usage & financial implications

5.21 The PBAC PSD for the previous submission stated that uptake rates were not well explained and likely to be an underestimate. In the minor resubmission, the PBS 10% sample data have been updated. The Sponsor stated that inaccuracies in the uptake rate will not result in any additional cost to Government.

5.22 The minor submission estimated a net saving to the PBS/RPBS of less than $10 million in Year 6 of listing, using effective prices, with a total net saving to the PBS/RPBS of $10 - $20 million over the first 6 years of listing. This is summarised in Table 4, as well as the expected prescription numbers.

5.23 The differences between the current resubmission and the previous submission with respect to the estimated usage and financial implications are as follows:

- The brolucizumab drug cost reflects the ranibizumab price (1:1 ratio), rather than a weighted price of aflibercept/ranibizumab;
- The injection substitution assumes an identical number of injections (1:1 dose relativity) for brolucizumab and aflibercept/ranibizumab, rather than trial-based dosing ([redacted]:6.03 brolucizumab:aflibercept/ranibizumab ratio).
- The MBS net cost is zero because there are no incremental costs associated with administration, rather than an incremental cost saving due to fewer brolucizumab injections;
- The brolucizumab drug cost is calculated using the current price of aflibercept and ranibizumab, rather than using the price prior to the F1 anniversary price reductions until expiration of the strategic agreement on 30 June 2022.

Table 4: 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]		359,586	380,124	401,313	417,787	435,427	449,887
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 displaced							
Aflibercept	2168D	73,989	100,805	125,054	144,064	161,906	171,808
Ranibizumab	10138N	42,317	54,985	64,422	70,715	75,724	76,528
Ranibizumab	1382R	1,528	1,349	1,085	825	612	433
Total		117,834	157,139	190,561	215,604	238,242	248,769
Estimated financial implications of treatment displaced (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		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous submission[c]		$3,976,505	$6,482,055	$3,348,958	-$470,795	-$589,537	-$699,020

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.
[c] As proposed by the Sponsor in the pre-PBAC response for the November 2019 submission (Table 7 of PSD). This financial estimate was calculated using (1) a weighted aflibercept/ranibizumab price for brolucizumab; (2) 1:1 dosing ratio; (3) MBS net cost of zero, consistent with 1:1 dosing ratio; and (4) brolucizumab price calculated using the aflibercept/ranibizumab prices prior to the F1 anniversary price reductions until expiration of the strategic agreement on 30 June 2022.

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

Financial Management – Risk Sharing Arrangements

5.25 The resubmission noted that ranibizumab and aflibercept are subject to risk sharing arrangements for the treatment of neovascular AMD. The resubmission stated that the degree to which these arrangements would, or would not, apply to brolucizumab is not known at this stage.

For more detail on PBAC's view, see section 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 noted the higher incidence of ocular serious adverse events (SAEs) reported for brolucizumab compared to aflibercept in the clinical studies and considered the claim of non-inferior safety was uncertain. The PBAC noted the anecdotal reports from the American Society of Retinal Specialists (ASRS) of retinal artery occlusion and intraocular inflammation since brolucizumab was approved in the United States, and considered that further review and clarity regarding the safety of brolucizumab is required.

6.2 The PBAC considered that the claim in the minor resubmission of non-inferior effectiveness of brolucizumab compared with aflibercept was reasonable based on two key trials (HAWK and HARRIER), and this was unchanged from its previous consideration in November 2019 (paragraph 5.10).

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 (paragraph 5.8) and considered this increased the uncertainty of the non-inferior safety claim.

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.

6.5 The PBAC noted that the minor resubmission had employed a 1:1 dose relativity in the cost-minimisation, consistent with the previous PBAC advice that there were no clinical reasons for dosing frequencies amongst brolucizumab and anti-VEGFs to be different to each other.

6.6 The PBAC noted that the Sponsor used the ranibizumab price for the CMA in the minor resubmission, based on ranibizumab being the least costly comparator (paragraphs 4.2 and 4.3). However, the PBAC considered that the CMA was not adequately supported as non-inferior safety of brolucizumab had not been established.

6.7 The PBAC noted that the minor resubmission estimated the listing of brolucizumab to be cost-saving to Government, notwithstanding the uncertain uptake rates over the first six years of listing (paragraphs 5.21 and 5.22).

6.8 The PBAC considered any future submission could be a minor resubmission and should address the uncertain claim of non-inferior safety.

6.9 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 is disappointed with the PBAC outcome but will continue to work collaboratively with the PBAC, the Department of Health and Federal Government to ensure that Australians with age-related macular degeneration receive access to Beovu through the Pharmaceutical Benefits Scheme (PBS) at the earliest opportunity.