PUBLIC SUMMARY DOCUMENT

Product: Ranibizumab, solution for intravitreal injection, 2.3 mg in 0.23 mL, Lucentis®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The re-submission sought to extend the current Authority required listing of ranibizumab to include treatment by an ophthalmologist, of a patient with visual impairment due to macular oedema secondary to retinal vein occlusion (both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO)).

2. Background

This was the second submission considered by the PBAC which sought to extend the listing of ranibizumab to include treatment of visual impairment due to macular oedema secondary to retinal vein occlusion.

At its November 2012 meeting, the PBAC rejected the submission on the basis of high and uncertain cost-effectiveness, which was likely to be substantially higher than that estimated in the submission.

The public summary document is available at the PBS website.

3. Registration Status

Ranibizumab is TGA registered for the following indications:
The treatment of neovascular (wet) age-related macular degeneration (AMD)
The treatment of visual impairment due to diabetic macular oedema (DME)
The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)

4. Listing Requested and PBAC's View

Authority required
Initial treatment by an ophthalmologist, of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

For BRVO visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) in the eye proposed for treatment.
For CRVO visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/320[a] (Snellen equivalent) in the eye proposed for treatment.

Authority required
Continuing treatment by an ophthalmologist, of visual impairment due to macular oedema secondary to retinal vein occlusion, where the patient has previously been granted an authority prescription.

Treatment is given monthly for six months. Consideration should be given to ceasing treatment if no response is seen after 3-4 injections. Thereafter, treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular oedema secondary to RVO (i.e. patient's BCVA is 20/40 or worse (Snellen equivalent) using ETDRS charts). Treatment is continued until stable visual acuity is reached for three consecutive monthly assessments.

The re-submission sought listing on the basis of superior comparative effectiveness and similar comparative safety compared with standard of care (laser photocoagulation and observation for patients with BRVO and observation only for patients with CRVO), using a cost-utility analysis.

5. Clinical Place for the Proposed Therapy

RVO is a blockage of the vessel which drains blood out of the retina, the light-sensitive tissue at the back of the eye. The blockage results in increased pressure within the blood vessel causing blood and fluid to leak from the blood vessels into the retina. This can result in swelling or thickening of the retina (oedema). Occlusions are categorised into branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) based on the site of the occlusion.

The current recommended treatment for BRVO patients with macular oedema and vision impairment is laser photocoagulation. For patients with CRVO current treatment is observation only. The re-submission proposed that ranibizumab would either replace or be co-administered with laser treatment in BRVO patients and replace observation in CRVO patients.

However, the PBAC noted the advice of the specialist during the Sponsor's hearing that bevacizumab is most commonly used in this treatment setting. The PBAC considered that it was likely that ranibizumab would replace a proportion of bevacizumab use.

6. Comparator

As in the November 2012 submission, the re-submission nominated laser photocoagulation and observation for patients with BRVO and observation only for patients with CRVO as the comparators.

The re-submission stated that bevacizumab was not TGA approved for RVO and was not formulated for intravitreal use and therefore the abovementioned comparators were considered appropriate.

As in November 2012, the PBAC considered that bevacizumab was a relevant comparator because bevacizumab is currently widely used for the treatment of BRVO and CRVO and is the therapy most likely to be replaced in practice. The PBAC accepted that laser photocoagulation + observation for patients with BRVO and observation only for patients with CRVO were also appropriate comparators.

The PBAC considered that the re-submission's argument, that bevacizumab is not TGA approved, nor formulated for intravitreal use, did not adequately address the fact that there is

unsubsidised use of bevacizumab for this indication, and therefore a comparison against it is relevant.

In considering the current re-submission, the PBAC noted head-to-head studies comparing ranibizumab and bevacizumab have been conducted. It also recalled advice from the specialists presenting at the Sponsor's hearings in both November 2012 and November 2013, that bevacizumab is currently widely used for treatment of RVO.

The PBAC considered it was important to resolve the issue of whether bevacizumab can be used as an appropriate comparator for ranibizumab, and if so, how a clinical and economic comparison versus bevacizumab could be conducted, and any implications of conducting such a comparison, given that bevacizumab is neither PBS-listed nor TGA-approved for the RVO indication. The PBAC requested the Department investigate these issues on its behalf.

7. Clinical Trials

The re-submission was based on the same trials presented in the November 2012 submission, BRAVO (N=397) and CRUISE (N=392). Both compared ranibizumab 0.3mg and 0.5mg with sham injection in patients with branch retinal vein occlusion and central retinal vein occlusion, respectively. The extension trial of BRAVO and CRUISE (HORIZON), presented in the November 2012 submission as supplementary evidence for the modelled evaluation, was again presented as supplementary evidence in this re-submission. Overall, the risk of bias in BRAVO and CRUISE is low, with little risk of selection bias, detection bias, attrition bias or reporting bias.

The details of the trials are presented in the table below.

Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Trial FVF4165g (BRAVO)	A phase III, multicentre, randomised, sham injection-controlled study of the efficacy and safety of Ranibizumab injection compared with sham in patients with macular edema secondary to branch retinal vein occlusion.	Final report July 2010
	Campochiaro, PA, Heier, JS, Feiner, L, *et al*. Ranibizumab for Macular Oedema following Branch Retinal Vein Occlusion: Six-month Primary end Point Results of a Phase III Study.	*Ophthalmology*, 2010; Vol 117(6): 1102-12
	Brown DM, Campochiaro PA, Bhisitkul RB *et al.* Sustained Benefits from Ranibizumab for Macular Oedema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study.	*Ophthalmology,* 2011; Vol 118(8):1594-1602

Trial ID	Protocol title/ Publication title	Publication citation
Trial FVF4166g (CRUISE)	A phase III, multicentre, randomised, sham injection-controlled study of the efficacy and safety of Ranibizumab injection compared with sham in patients with macular oedema secondary to central retinal vein occlusion.	Final Report August 2010
	Brown, DM, Campochiaro, PA, Singh, RP, *et al.* Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Six-Month Primary End Point Results of a Phase III Study.	*Ophthalmology,* 2010; Vol 117(6): 1124-33
	Campochiaro PA, Brown DM, Awh CC et al. Sustained Benefits from Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study.	*Ophthalmology* 2011; Vol 118(10): 2041-2049
Supplementary randomised trial		
Trial FVF3426g (HORIZON)	An open-label, multicentre extension study to evaluate the safety and tolerability of ranibizumab in subjects with macular oedema secondary to retinal vein occlusion (RVO) who have completed a Genentech-sponsored ranibizumab study (either BRAVO or CRUISE).	May 2011
	Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, et al. Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Long-term Follow-up in the HORIZON trial.	*Ophthalmology,* 2012; Vol 119(4): 802-809

8. Results of Trials

The results presented in the re-submission were unchanged from those presented in the November 2012 submission

The PBAC recalled that in November 2012, it had accepted that ranibizumab is associated with a statistically significant gain in best corrected visual acuity (BCVA) in the treated eye over sham injection over the 6-month duration of the head-to-head comparison with a mean difference of 10.6 letters for BRVO and of 13.8 letters for CRVO.

Summary of key results from BRAVO and CRUISE

Change in BCVA	SHAM	Ranibizumab 0.5mg		Ranibizumab 0.3mg	
	Change from baseline	Change from baseline	Difference vs. sham	Change from baseline	Difference vs. sham
BRAVO	N=132 7.3 (5.1, 9.5)	N=131 18.3 (16.0, 20.6)	10.6 (7.6, 13.6)	N=134 16.6 (14.7,18.5)	9.4 (6.6, 12.2)
CRUISE	N=130 0.8 (-2.0, 3.6)	N=130 14.9 (2.6, 17.2)	13.8 (10.3,17.4)	N=132 12.7 (9.9; 15.4)	11.5 (7.7,15.3)

BCVA=best corrected visual acuity

The PBAC clarified that the overall clinical meaningfulness of an improvement in the treated eye will depend on the baseline visual acuity (VA) of the patient in both eyes and on the subsequent overall visual acuity during and after treatment.

Overall, the PBAC accepted that ranibizumab is an effective treatment for visual impairment due to RVO, but remained concerned about the extent of clinically relevant improvement in overall BCVA.

The safety data from the November 2012 submission was unchanged in this re-submission. The re-submission maintained that the overall incidence of adverse events was similar across treatment groups. The PBAC did not agree with the November 2012 submission's claim, noting that in both trials there were more conjunctival haemorrhages (RD=12.6%; 95% CI: 0.6, 24.7) and retinal exudates (RD=10.9%; 95% CI: 1.4, 20.3) for ranibizumab compared with sham injections, with the differences being statistically significantly in the BRAVO trial.

A summary of benefits and harms for ranibizumab versus sham injection using the secondary outcome of gain ≥15 letters and loss <15 letters for benefits is provided in the table below.

Summary of comparative benefits and harms for ranibizumab and sham injection

Trial	Ranibizumab 0.5mg	Sham Injection	RR* (95% CI)	Event rate/100 patients at 12 months		RD* (95% CI)
				Ranibizumab:	Sham Injection	
Benefits						
Gain ≥15 letters at 12 months						
BRAVO (BRVO)	79/131	58/132	1.37 (1.09, 1.75)	60.3	43.9	0.16 (0.04, 0.28)
CRUISE (CRVO)	66/130	43/130	1.53 (1.15, 2.08)	50.8	33.1	0.18 (0.06, 0.29)
Loss < 15 letters at 12 months						
BRAVO (BRVO)	128/131	124/132	1.04 (0.99, 1.11)	97.7	93.9	0.04 (-0.01, 0.27)
CRUISE (CRVO)	127/130	117/130	1.09 (1.02, 1.17)	97.7	90.0	0.08 (0.02, 0.14)
Harms						
Eye pain						
BRAVO (BRVO)	21/130	19/131	1.11 (0.63, 1.96)	16.2	14.5	0.017 (-0.072, 0.106)
CRUISE (CRVO)	24/129	13/129	1.85 (1.00, 3.45)	18.6	10.1	0.085 (-0.00, 0.173)
Conjunctival haemorrhage						
BRAVO (BRVO)	71/130	55/131	1.30 (1.01, 1.69)	54.6	42.0	0.126 (0.006, 0.244)
CRUISE (CRVO)	53/129	42/129	1.26 (0.92, 1.75)	41.1	32.6	0.085 (-0.033, 0.201)
Retinal exudates						
BRAVO (BRVO)	32/130	18/131	1.79 (1.07, 3.02)	24.6	13.7	0.109 (0.013, 0.205)
CRUISE (CRVO)	22/129	15/129	1.47 (0.81, 2.69)	17.1	11.6	0.054 (-0.032, 0.142)

*RR and RD calculated using Stats Direct Version 2.7.9
BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion

The PBAC noted that based on these trials, for every 100 patients treated with ranibizumab compared to sham injection:

- Approximately 16 to 18 patients would experience a gain of at least 15 letters in visual acuity (from baseline at 12 months);
- Approximately 4 to 8 patients would experience a loss of less than 15 letters in visual acuity (from baseline at 12 months);
- Approximately 2 to 9 patients would experience eye pain;
- Approximately 9 to 12 patients would experience conjunctival haemorrhage; and
- Approximately 5 to 11 patients would experience retinal exudates

The PBAC noted the perspective of the ophthalmologist's presentation during the sponsor's hearing in relation to visual acuity, vision related quality of life, bilateral treatment, current use of bevacizumab and other clinical matters in response to the Committee's questions.

9. Clinical Claim

The re-submission claimed that ranibizumab has superior effectiveness with a similar safety profile compared to standard of care, consistent with the claims in the November 2012 submission . The PBAC agreed with the claim that ranibizumab has superior effectiveness over laser treatment for BRVO and superior effectiveness over observation for CRVO, but did not agree with the claim for similar safety. The PBAC saw no reason to change its previous conclusion in its consideration of the re-submission.

10. Economic Analysis

The re-submission presented an updated cost-utility analysis based on the claim of superior effectiveness and similar safety of ranibizumab compared to standard of care. The results for the individual BRVO and CRVO models were incremental costs per quality adjusted life year (QALY) of between $45,000 and $75,000 for BRVO and between $15,000 and $45,000for CRVO.

The PBAC noted that while the requested price of ranibizumab had been reduced from that requested in the November 2012 submission the number of health states had decreased from 9 to 5 and the utility values had changed, the corrected base case ICER was very similar to the base case ICER in the November 2012 model.

The PBAC noted that the utility values used in the model were derived from the RESTORE trial for diabetic macular oedema (DME) and were weighted for best/worst seeing eye in the RVO trials.

However, the PBAC agreed with the Economic Sub-Committee (ESC) that the utilities drawn from the RESTORE trial have the same issue in their application in this model as in the previous submission and in the corresponding re-submission requesting a listing for use of ranibizumab in diabetic macular edema (DME). The PBAC recalled its previous concerns regarding the translation between trial-based visual acuity differences across treated eyes and modelled utility differences for patients overall (which will depend on visual acuity (VA) in both eyes, and in particular, in the better seeing eye). These concerns affect claims of decreased falls and decreased mortality as well as increased utility. These claimed effects were all assumed to arise from a correlation with the demonstrated differences in VA effects

on treated eyes between anti-VEGF treatments and controls. However, the ESC advised that the VA of the better seeing eye is more likely to correlate with a patient's utility, risk of falls and risk of mortality. Noting that data from the RESTORE trial were used to identify whether a patient's treated eye was the patient's better or worse seeing eye, and that such data were available at both baseline and after twelve months' follow up, the ESC requested the sponsor provide additional data to better inform the PBAC's deliberations. These were provided in the sponsor's Pre-PBAC Response.

The PBAC accepted the advice of the ESC that claims for differences in utility should be limited to those differences in proportions for the following groups of patients because it is only in these patients where the effect on the treated eye's VA might have a direct and discernible effect on overall VA by improving the VA of the better seeing eye:

- patients in whom the treated eye was the better seeing eye after 12 months follow-up, where the treated eye was originally the worse seeing eye;
- patients in whom the difference in VA between eyes was greater after twelve months follow-up compared to baseline, where the treated eye was originally the better seeing eye; and
- patients in whom VA was discernibly better for the treated eye after twelve months' follow-up.

The PBAC also considered that the re-submission did not adequately justify the use of utility values based on a DME population for patients with RVO.

The PBAC noted that the transitions between the health states, and therefore the health states themselves, were based on the VA data for the treated eye. Differences in these transitions across the ranibizumab and comparator arms of the model simulate and then extrapolate the treatment effect on VA detected in the trials for the treated eye. As there is no plausible basis to expect any treatment effect to use in a model for the other eye, a model with transitions and health states for the other eye would have no basis for any treatment effect on VA. The difficulty in interpreting the model based on the treated eye as presented is the transformation from VA to utilities (and thus QALYs), when utilities are based on the perceptions of the whole patient which is influenced by perceptions of overall VA, not perceptions of the treated eye's VA. The attempt in the re-submission to adjust for VA across both eyes for the purpose of mapping to utilities does not address this fundamental misalignment between the design of the model based on treated eye VA and overall patient utilities. For the same reason, simply halving the claimed utility to account for a full VA effect in one eye and no VA effect in the other eye would also not address this issue.

Overall, the PBAC considered the model to be unsuitable as a basis for determining the cost-effectiveness of ranibizumab in the requested treatment setting. The mapping approach in the submission to estimate utilities is only valid if it is applied to health states that reflect the overall VA of patients, not health states that reflect the treated eye.

The PBAC considered that, as overall VA is influenced mostly by the better seeing eye, the potential for utility differences to arise is influenced by the proportions of worse and better seeing eyes which are treated. The data requested by ESC goes some way towards identifying the proportions of patients for which overall VA differences would be perceptible for patients across the two arms of the model. This approach might help redevelop the model so that it is

based on patient-perceptible transitions in and health states of overall VA, which would provide a more plausible basis for the transformation to utilities.

The PBAC considered various means by which it might be possible to construct a comparison with bevacizumab, and whether a cost-minimisation analysis would be possible. However, the PBAC noted that it had not assessed the cost-effectiveness of bevacizumab in this setting, nor had equi-effective doses of bevacizumab and ranibizumab been determined. The PBAC also sought advice from the department on the issue of the appropriate basis for ascertaining the unit cost of bevacizumab for each time it is injected in the eye. The PBAC noted therefore that it was not possible to set an appropriate price for ranibizumab without this information.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated that the number of patients (BRVO and CRVO) likely to be treated with ranibizumab is in Year 5 of listing was less than 10,000. The PBAC noted that these estimates were less than the November 2012 estimates, due to a reduction in the proportion of prevalent patients initiating treatment. The net cost to the PBS/RPBS was estimated to be in the range of $10-30 million in Year 5 of listing, with a net cost to Government in the first five years of listing of between $30-60 million.

The PBAC noted that the re-submission acknowledges that there is some uncertainty associated with injection numbers.

12. Recommendation and Reasons

The PBAC deferred making a recommendation in relation to the re-submission for ranibizumab for treatment of visual impairment due to macular oedema secondary to retinal vein occlusion due to unresolved concerns regarding the appropriate comparator, and the unsuitability of the submitted model as a basis for determining the cost-effectiveness of ranibizumab in the requested treatment setting.

The PBAC noted that randomised head-to-head studies comparing ranibizumab and bevacizumab have been conducted. It also recalled the repeated advice from the specialists presenting during the Sponsor's hearings in both November 2012 and November 2013, that bevacizumab is currently widely used for treatment of RVO.

The PBAC considered it was important to resolve the issue of whether bevacizumab can be used as an appropriate comparator for ranibizumab, and if so, how a clinical and economic comparison versus bevacizumab could be conducted, and any implications of conducting such a comparison given that bevacizumab is neither PBS-listed nor TGA-approved for the RVO indication. The PBAC requested the Department investigate these issues on its behalf.

The PBAC accepted that ranibizumab is an effective treatment for visual impairment due to RVO.

The PBAC considered that the revised economic model presented in the re-submission was not suitable for the purpose of determining the cost-effectiveness of ranibizumab in the requested treatment setting, as it was driven by improvements in VA in the treated eye. The PBAC shared the ESC's concerns regarding the translation between trial-based VA

differences as measured in treated eyes and modelled impacts on utility for patients (which will depend on VA in both eyes, and in particular, in the better seeing eye).

The PBAC noted that utility, risk of falls and risk of mortality depends on VA in both eyes, and therefore the impact of an improvement in VA in the treated eye will depend on the overall impact on VA in both eyes, and what changes are perceptible to the patient. The PBAC considered that utility gains from improvement in VA in the treated eye instead of in patients were not appropriate for estimating cost-effectiveness of ranibizumab. The PBAC suggested that the sponsor redevelop the model to address these concerns.

The PBAC noted that MSAC were pursuing resolution of issues associated with use of optical coherence tomography (OCT) testing in relation to the use of ranibizumab. However, the ongoing assessment of OCT testing by MSAC was not a major factor in the PBAC's decision to defer the current re-submission.

Outcome:
Deferred

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor will continue to work with the PBAC to ensure listing of ranibizumab for retinal vein occulsion but firmly believes that bevacizumab is not an appropriate comparator.