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 2012

1. Purpose of Application

The submission sought to extend the current Authority Required listing of ranibizumab to include the initial and continuing treatment by an ophthalmologist, of visual impairment due to macular oedema secondary to retinal vein occlusion.

2. Background

The PBAC had not previously considered ranibizumab in the treatment of vision impairment due to macular oedema secondary to retinal vein occlusion.

Ranibizumab is currently PBS-listed for subfoveal choroidal neovascularisation due to age-related macular degeneration.

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 retinal vein occlusion.

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.

Continuing treatment by an ophthalmologist, of visual impairment due to macular oedema secondary to retinal vein occlusion, in patients who had received treatment with ranibizumab prior to the [date of PBS listing].

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Retinal vein occlusion is an obstruction of the veins draining blood from the back of the eye, caused by a blood clot (thrombus) or other possible causes such as external compression of the vein or diseases of the vessel wall. Obstruction of one or more of the retinal veins causes blood and fluid to leak from the capillaries that drain into the obstructed vein. This can result in swelling or thickening of the retina (oedema). Damage to the capillary bed can result in an area of the retina becoming non-perfused (i.e. ischaemic).

Retinal vein occlusion is classified into branch (BRVO) and central (CRVO) based on the site of venous occlusion: CRVO implies an occlusion of the central retinal vein and BRVO implies an occlusion of the branch retinal vein.

The condition is predominantly unilateral (i.e. affects one side only).

BRVO and CRVO can be subdivided into two subtypes: perfused (non-ischaemic) and non-perfused (ischaemic).

The current recommended treatment for ischaemic and non-ischaemic BRVO patients with macular oedema and vision impairment is laser photocoagulation. Whilst for patients with CRVO (ischaemic and non-ischaemic) current treatment is observation only. It was anticipated that ranibizumab would either replace or be co-administered with laser treatment in BRVO patients and replace observation in CRVO patients.

6. Comparator

The submission nominated laser photocoagulation and observation for patients with BRVO and observation only for patients with CRVO. These were appropriate comparators. However, the PBAC considered that bevacizumab is a relevant comparator because it is currently widely used for the treatment of BRVO and CRVO and is the therapy most likely to be replaced in practice. Bevacizumab is not TGA approved for RVO and is not formulated for intravitreal use. Further, the cost-effectiveness of bevacizumab for RVO is not known because it has not been considered by the PBAC. Thus it would be necessary to establish the evidence base for and cost-effectiveness of this comparator as a first step to then establish the incremental cost-effectiveness of ranibizumab against it.

7. Clinical Trials

The submission presented two randomised trials, BRAVO (patients with BRVO) and CRUISE (patients with CRVO), comparing ranibizumab 0.5 mg, 0.3 mg and sham injections (injection of placebo) in 789 patients with vision impairment due to macular oedema secondary to retinal vein occlusion (either BRVO or CRVO). Injections were administered monthly for six months. In both clinical trials, BRAVO and CRUISE, sham injections were non-penetrative. Within the BRAVO trial patients in all groups were provided rescue laser photocoagulation treatment (at 6 months, 54.5% of the sham injection arm compared to 18.7% and 19.8% in the 0.3 mg and 0.5 mg ranibizumab arms respectively). In the CRUISE trial laser treatment was not administered as it is not a recommended treatment in patients with CRVO. Both trials consisted of a 6-month treatment phase after which there was a 6-month observation phase where patients in the ranibizumab arms were administered on an as required basis and those in the sham arm were administered ranibizumab 0.5 mg on a prn (when required) basis. In both trials the poorer seeing eye was treated.

The table below details the published trials presented in the submission.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Trial FVF4165g (BRAVO) Campochiaro PA et al. Brown DM et al.	 Ranibizumab for Macular Oedema following Branch Retinal Vein Occlusion: Six-month Primary end Point Results of a Phase III Study. Sustained Benefits from Ranibizumab for Macular Oedema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study.	 *Ophthalmology* (2010); 117(6): 1102-12 *Ophthalmology* (2011); 118(8):1594-1602
Trial FVF4166g (CRUISE) Brown DM et al. Campochiaro PA et al.	 Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Six-Month Primary End Point Results of a Phase III Study. Sustained Benefits from Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study.	 *Ophthalmology* (2010); 117(6): 1124-33 *Ophthalmology* (2011); 118(10): 2041-2049
Trial ROCC Kinge B et al.	 Efficacy of Ranibizumab in Patients with Macular Oedema Secondary to Central Retinal Vein Occlusion: Results from the Sham-Controlled ROCC Study.	 *American Journal of Ophthalmology* (2010); September: 310-314
Supplementary randomised trial(s)		
Trial FVF3426g (HORIZON) Heier JS et al.	 Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Long-term Follow-up in the HORIZON trial.	 *Ophthalmology* (2012); 119(4): 802-809

A meta-analysis of ROCC and CRUISE trials was provided within the submission. The BRAVO trial was not included in the meta-analysis as this trial was for BRVO compared to CRVO as assessed in the ROCC and CRUISE trials.

8. Results of Trials

The primary outcome for both trials was the mean change in best corrected visual acuity (BCVA) and the proportion of patients who gained or lost the ability to read fifteen letters or more in the same scale. These outcomes were measured in the treated eye only and bilateral visual acuity was not reported. Although there is no widely accepted minimally clinically important difference in BCVA, both clinical trials were powered to identify a statistically significant difference of ten letters between ranibizumab 0.5 mg and sham injections.

The primary outcome results from the direct randomised trials are summarised below.

Results of mean change from baseline in BCVA (number of letters) to Month 6 across the direct randomised trials

Trial ID	Ranibizumab		Sham	Mean difference	
	0.5 mg MD (95% CI)	**0.3 mg MD (95% CI)**	**MD (95% CI)**	**0.5 mg vs. Sham[b] (95% CI)**	**0.3 mg vs. Sham[b] (95% CI)**
BRAVO[a], n	131	134	132		
	18.3 (16.0 – 20.6)	16.6 (14.7 – 18.5)	7.3 (5.1 – 9.5)	**10.6 (7.6 – 13.6)**	**9.4 (6.6 – 12.2)**
CRUISE, n	130	132	130		
	14.9 (12.6 – 17.2)	12.7 (9.9 – 15.4)	0.8 (-2.0 – 3.6)	**13.8 (10.3 – 17.4)**	**11.5 (7.7 – 15.3)**

Bold = statistically significant; CI = confidence interval; Sham = sham injections; MD = mean difference in least squares; BCVA = best corrected visual acuity

[a] Rescue laser treatment was available to patients in all treatment groups

[b] difference based on pair-wise ANOVA models adjusted for baseline visual acuity score

Ranibizumab was associated with a statistically significant gain in BCVA in the treated eye over the 6 months' duration of the head to head comparison (mean difference of 10.6 letters [95% CI: 7.6 to 13.6 letters] for BRVO; and 13.8 letters [95% CI: 10.3 to 17.4 letters] for CRVO).

For the proportion of patients who gained 15 letters or more, or, lost less than 15 letters in BCVA score at month 6 in the BRAVO and CRUISE trials, the risk difference between ranibizumab 0.5 mg and sham injections favoured ranibizumab 0.5 mg, although the result was not statistically significant in the BRAVO trial for patients who lost less than 15 letters from baseline .

For PBAC's view, see Recommendation and Reasons.

The following table summarises the key adverse events (as identified within the direct randomised trials).

	Ranibizumab			
Trial / Adverse event	**0.5 mg n event (%)**	**0.3 mg n event (%)**	**Sham n event (%)**	**0.5 mg vs. Sham RD (95% CI)**
BRAVO	N=130	N=134	N=131	
Any ocular events	106 (81.5%)	112 (81.5%)	101 (77.1%)	4% (-5.4%, 14.3%)
Conjunctival hemorrhage	71 (54.6%)	80 (59.7%)	55 (42.0%)	**12.6% (0.6%, 24.7%)**
Myodesopsia	6 (4.6%)	17 (12.7%)	1 (0.8%)	3.9% (-0.1%, 7.8%)
Retinal exudates	32 (24.6%)	34 (25.4%)	18 (13.7%)	**10.9% (1.4%, 20.3%)**
Serious ocular event	2 (1.5%)	3 (2.2%)	2 (1.5%)	0%
Any non-ocular event	70 (53.8%	80 (59.7%	71 (54.2%)	-0.4% (-12%, 11.7%)
Arterial thromboembolic	3 (2.3%)	1 (0.7%)	1 (0.8%)	1.5% (-1.4%, 4.5%)
Serious non-ocular event	12 (9.2%)	11/ (8.2%)	5 (3.8%)	5.4% (-0.5%, 11.4%)
CRUISE	N=129	N=132	N=129	
Any ocular events	104 (80.6%)	103 (78.0%)	99 (76.7%)	3.9% (-6.1%, 13.9%)
Conjunctival hemorrhage	53 (41.1%)	57 (43.2%)	42 (32.6%)	8.5% (-3.2%, 20.3%)
Myodesopsia	12 (9.3%)	9 (6.8%)	5 (3.9%)	5.4% (-0.6%, 11.4%)
Retinal exudates	22 (17.1%)	35 (26.5%)	15 (11.6%)	5.4% (-3.1%, 14.0%)
Serious ocular event	2 (76.7%)	4 (3.0%)	6 (4.7%)	-3.1% (-7.3%, 1.1%)
Any non-ocular event	67 (51.9%)	60 (45.5%)	63 (48.8%)	3.1% (-9.1%, 15.3%)
Arterial thromboembolic	4 (3.1%)	2 (1.5%)	2 (1.6%)	1.6% (-2.1%, 5.2%)
Serious non-ocular event	11 (48.8%)	12 (9.1%)	10 (7.8%)	0.8% (-5.9%, 7.4%)

Bold = statistically significant; CI = confidence interval; Italics = calculated during evaluation; Ranibiz

= Ranibizumab; RD = risk difference;

In the BRAVO trial, the ranibizumab 0.5 mg group had statistically significantly more conjunctival haemorrhage (RD: 12.6%; 95% CI: 0.6%, 24.7%) and retinal exudates than the sham injection group (RD: 10.9%; 95% CI: 1.4%, 20.3%).

The submission claimed that subconjunctival haemorrhages are aesthetic, resolve without treatment within one or two weeks when the blood is reabsorbed and are considered to be of no clinical relevance. Similarly, retinal exudates are commonly observed when oedema resolves and are not associated with any detrimental effects in RVO. These adverse events are expected and not serious, and require no additional treatment.

The safety profile of treating patients with vision impairment due to macular oedema secondary to retinal vein occlusion was consistent with the known safety profile of ranibizumab.

9. Clinical Claim

The submission described ranibizumab as superior in terms of comparative effectiveness and similar in terms of comparative safety over laser treatment in BRVO and placebo in CRVO.

The claim for comparative effectiveness against observation or laser photocoagulation in the trials was considered reasonable, but based on measurement of visual acuity in the treated eye only.

The PBAC did not agree with the claim that ranibizumab is similar in terms of comparative safety to the comparators.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A modelled cost utility analysis based on superiority claim for comparative benefit was presented. Two separate models were constructed: one for BRVO and one for CRVO. Transitions within the models continued until the end of the model duration, which was 120 months (i.e. 10 years). Drug and laser costs were based on the mean numbers of ranibizumab injections (5.7 in BRAVO and 5.6 in CRUISE) and laser treatments (21.4% of 0.5 mg ranibizumab and 57.6% of sham injection patients in BRAVO) in the respective study arms at 6 months.

An overall incremental cost effectiveness ratio in the range of $15,000 - $45,000/extra QALY gained was claimed based on the weighted average of the BRVO and CRVO modelled costs and QALY outputs.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost per year to the PBS to be in the range of $10 - $30 million in Year 5.

For PBAC's view, see Recommendations and Reasons.

12. Recommendation and Reasons

The PBAC noted that branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) usually manifest as unilateral diseases, that is, they usually affect one eye and not the other. The natural history of RVO has an acute phase involving macular oedema following the vein occlusion, with long-term outcomes affected by damage to the retina occurring during the acute phase. The objective of treatment in the acute phase is to minimise acute damage associated with oedema whilst allowing collateral vessels to develop. This is expected to improve long-term prognosis of visual acuity.

The PBAC considered that bevacizumab is a relevant comparator because it is currently widely used for the treatment of BRVO and CRVO and is the therapy most likely to be replaced in practice. However bevacizumab is not TGA approved for RVO and is not formulated for intravitreal use. Further, the cost-effectiveness of bevacizumab for RVO is not known because it has not been considered by the PBAC. Thus it would be necessary to establish the evidence base for and cost-effectiveness of this comparator as a first step to then establish the incremental cost-effectiveness of ranibizumab against it. For these reasons, the PBAC also accepted laser photocoagulation plus observation for patients with BRVO, and observation only for patients with CRVO, to be appropriate comparators for ranibizumab as presented in the submission.

The submission presented two randomised trials, BRAVO and CRUISE, for patients with BRVO and CRVO respectively. Both trials compared ranibizumab 0.5 mg, ranibizumab 0.3 mg or sham injections when given monthly for 6 months with the patient and the outcomes assessor masked to the patient's treatment assignment. Laser photocoagulation rescue therapy was permitted in BRAVO. The primary outcome for BRAVO and CVRO was the mean change in best corrected visual acuity (BCVA) in the treated eye at 6 months measured as the number of letters on a standard eye chart. A 6-month unmasked observational period followed for both trials where all patients were treated with ranibizumab on a when required basis, including patients originally randomised to sham, who received ranibizumab 0.5 mg after the initial blinded period of 6 months in the trial.

The PBAC agreed that ranibizumab is associated with a statistically significant gain in BCVA in the treated eye over the 6 months' duration of the head to head comparison (mean difference of 10.6 letters [95% CI: 7.6 to 13.6 letters] for BRVO; and 13.8 letters [95% CI: 10.3 to 17.4 letters] for CRVO). The PBAC agreed that a greater extent of improvement was reasonable for CRVO compared with BRVO because the PBAC considered that BRVO is potentially subject to some natural return of vision (Sham-treated patients with BRVO had an improvement of 7.3 letters; 95% CI: 5.1 to 9.5 letters, comparing results at 6 months for the sham-treated eye with the baseline for this group) and laser therapy was also offered on a 'as needed' basis for these patients (more than 54% of Sham-treated patients also received laser in the 6-month treatment period). The PBAC noted that there was no statistically significant difference in outcomes across the 0.5 mg and 0.3 mg doses for either BRVO or CRVO. The economic model was based on only the 0.5 mg dose.

Beyond 6 months there are no comparative data, although non-comparative data are available from a 6-month open-label period which allowed cross-over from sham treatment to ranibizumab. From the response of sham treated patients who crossed over to ranibizumab 0.5 mg in the 6-month open-label phase of the trials, the PBAC also noted that the extent of

benefit appears to be reduced if treatment is delayed: comparing an improvement of 12.1 letters at 12 months with an improvement of 7.3 letters at 6 months for BRVO and comparing an improvement of 7.3 letters at 12 months with an improvement of 0.8 letters at 6 months for CRVO.

The PBAC did not agree with the claim that ranibizumab is similar in terms of comparative safety to the comparators. In both trials, there were more conjunctival haemorrhages and retinal exudates for ranibizumab compared with sham injections, with the differences being statistically significantly in the BRAVO trial. The PBAC noted the sponsor's comments that these are of short duration and do not require additional treatment.

The PBAC noted that optical coherence tomography (OCT), with a threshold of mean central subfield thickness of greater than or equal to 250 micrometres, was used as an essential part of determining eligibility for inclusion into both ranibizumab trials, for determining the need for rescue interventions in the BRVO trial, and for determining the need for ranibizumab re-injection after six months in both trials. However, the PBAC was aware that OCT is not currently subsidised through the MBS, and so policy issues would arise for the government if a PBS restriction were to refer to OCT to determine initial or continuing eligibility for ranibizumab or its competitor aflibercept if either were to be recommended for PBS listing. The PBAC therefore requested advice from the Medical Services Advisory Committee (MSAC), as identified in the Economics Sub-Committee and Drug Utilisation Sub-Committee advice, on the use of OCT firstly to establish the extent of baseline severity of RVO to help determine the eligibility of patients for ranibizumab and secondly to monitor RVO to guide the frequency of subsequent injections. In particular, advice was sought on any changes to the extents to which OCT (and the more invasive fluorescein angiography) would be used in managing RVO as a result of new injectable therapies compared to current treatment modalities and on what additional information is provided by OCT over fluorescein angiography alone, in ascertaining the severity of disease when determining eligibility for and particularly frequency of dosing with the new injectable therapies.

The PBAC considered that the restriction would require revision once the outstanding issues regarding OCT have been resolved. The PBAC noted the advice provided by its subcommittees regarding the restriction including the method of diagnosis and monitoring of RVO, definition of visual impairment (the BRVO and CRVO trials specified different BCVA thresholds as eligibility criteria), and whether the restriction should be limited to recently diagnosed patients (the BRVO and CRVO trials both specified a 28-day screening period before randomisation and excluded patients with a time from diagnosis of greater than 12 months).

The PBAC noted that the clinical trial data for visual acuity related to the treated eye only. The visual characteristics of the other eye or measurement of binocular vision were not reported in the submission. The PBAC considered this important in the context of assessing cost-effectiveness, which needs to be from the perspective of the patient overall, not limited to the treated eye. The PBAC noted that it may be desirable to treat unilateral ocular conditions. However the submission's translation of the improvements in the treated eye to the economic model does not take account of the fact that the other eye also contributes to the patient's overall visual acuity, functioning and quality of life. Rather, the model translates the extent of improvements in the treated eye as though they represented the extent of improvements in the patient's overall visual acuity and thus translated to the extents of

improvement in functioning and quality of life. However the untreated eye, with better initial visual acuity, is not expected to improve and so the overall translation on functioning and quality of life is overestimated by the submission's approach. Overall, the PBAC agreed that treating the poorer eye results in improvements in its visual acuity, but that the submission's approach overestimates the extent of any consequential improvements in patient-perceived functioning and quality of life.

The Committee concluded that both models were sensitive to the time horizon in the model and considered that there is no evidentiary basis to accept the 10-year extrapolation. The trials provided only 6 months of comparative data for visual acuity, with subsequent 6 months' open-label follow-up with cross-over from sham to ranibizumab and then a 12-month extension study. This provided weak support for the transition probabilities assumed for the model and also for the assumption in the economic model of sustained incremental visual acuity in the treated eye for ten years. The assumption of such persistence of benefit is likely to be optimistic.

The model also relies on a series of poorly supported assumptions to translate from visual acuity in the treated eye to QALY gains for the treated patient. As noted above, the PBAC considered that the utility values applied in the base case economic model for the visual acuity improvement in the treated eye overestimated the true utility impact for patients whose overall visual acuity is also affected by the visual acuity in the other eye. In addition, the utilities used for the model were drawn from one source. The PBAC considered that the applicability of this source to the proposed PBS population had not been adequately addressed in the submission. The PBAC noted the variability in utilities across the base case (relying on the time trade-off results from the one source applied to the improvements for the treated eye as though they represented the improvements for the patient's overall visual acuity) and the less favourable results in the sensitivity analyses (one relying on the standard gamble results from the one source applied to the improvements for the treated eye as though they represented the improvements for the patient's overall visual acuity, and the other relying on results from another source which assumes the extreme cases of perfect utility for visual acuity categories 1-4 and complete blindness in the treated eye for visual acuity categories 5-8). The PBAC also considered that utility gains for macular degeneration, presented as a sensitivity analysis in the submission, cannot be directly applied for RVO, which is a unilateral condition to a greater extent than macular degeneration.

Similarly, the PBAC considered that the reductions in the rates of falls (with associated cost offsets) and reductions in mortality rates had been overestimated, because the likelihood of falling or dying is related to changes in a patient's overall visual acuity, not just changes in the visual acuity of the treated eye.

The PBAC acknowledged the sponsor's comments that visual acuity does not return completely in patients with BRVO. However the PBAC remain concerned that the economic model does not adequately capture the natural history of the disease and the extent to which overall visual acuity may return.

The PBAC agreed with the DUSC that the estimates of use were overestimated particularly in Year 1. The PBAC also remained concerned about wastage given that the requested 2.3 mg vial is intended for each 0.5 mg dose.

The PBAC considered that the risk share arrangement offered in the submission favours the sponsor. Comparative evidence of the benefit of ranibizumab over the accepted comparator is available only for 6 months (up to six injections if administered monthly). The financial analyses assume an average number of injections for BRVO and for CRVO that are not consistent with 6 months of trial data.

Overall the PBAC concluded that the revised weighted ICER across BRVO and CRVO in the range of $45,000 - $75,000 is high and likely to be substantially higher than presented in the submission because the benefits to the patient of treating RVO, a unilateral ocular condition, has been overestimated in the submission. The assumed maintenance of benefit over the 10-year time horizon of the model is also inadequately supported and a likely overestimate.

The PBAC therefore rejected the submission on the basis of high and uncertain cost effectiveness, which is likely to be substantially higher that estimated in the submission.

Recommendation:
Reject

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

Novartis will continue to work with the PBAC to resolve the issues in order to make ranibizumab available on the PBS to patients with vision impairment due to RVO.