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 diabetic macular oedema (DME), as diagnosed by fluorescein angiography.

2. Background

This was the second submission considered by the PBAC seeking to extend the listing of ranibizumab to include treatment of visual impairment due to DME.

At its March 2013 meeting, the PBAC rejected a submission on the basis of uncertainty about the incremental cost-effectiveness ratio (ICER), the comparative safety and lack of clarity in the extent of benefit measured as an average difference of five letters for the treated eye. The public summary document for the March 2013 PBAC meeting is available on 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).

The registration of ranibizumab for treatment of visual impairment due to DME was approved by the TGA in August 2011.

4. Listing Requested and PBAC's View

Authority required

Initial treatment by an ophthalmologist, of visual impairment due to diabetic macular oedema, as diagnosed by fluorescein angiography. Visual impairment is defined as best corrected visual acuity score between 78 and 39 based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts administered at a distance of 4 metres (approximate Snellen equivalent 20/32-20/160).

Continuing treatment either as monotherapy or in combination with laser photocoagulation by an ophthalmologist, of visual impairment due to diabetic macular oedema, where the patient has previously been granted an authority prescription for the same eye. Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to

DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than one month.

The re-submission sought listing on the basis of superior comparative effectiveness and equivalent comparative safety compared with laser photocoagulation, using a cost-utility analysis.

The PBAC agreed with the Economic Sub-Committee (ESC) that the eligibility criteria to initiate treatment based on visual acuity (VA) scores were broad and were likely to allow most older people to access treatment. The PBAC also agreed that the criteria for continuing treatment were subjective and would be difficult to implement in the restriction.

The PBAC noted that the trial data supported the view that baseline VA is a factor in determining response to treatment. Patients commencing treatment with good VA are unlikely to show substantial improvement (i.e., they remain stable), whereas those with poorer baseline vision may be more likely to show an improvement that is clinically relevant.

5. Clinical Place for the Proposed Therapy

DME is a complication of diabetic retinopathy. It is diagnosed by ophthalmic examination, fluorescein angiography and fundus photography. When DME affects the centre of the macula, it can lead to loss of visual acuity, and if left untreated, to blindness. The natural progression of DME leads to a significant loss (≥10 letters) within two years in 50% of individuals.

The re-submission proposed that ranibizumab will replace laser photocoagulation and will be used as first-line treatment for visual impairment due to DME. 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.

The PBAC noted that the proposed restriction specifies that ranibizumab could be used as monotherapy or in conjunction with laser photocoagulation, but that only monotherapy treatment was included in the economic evaluation and financial estimates in the re-submission.

6. Comparator

As in the March 2013 submission, the re-submission nominated laser treatment as the main comparator.

In its March 2013 consideration, the PBAC accepted that laser treatment was the appropriate comparator if ranibizumab is used as monotherapy. However, the PBAC also considered that bevacizumab was also a relevant comparator, despite not being TGA approved for the DME indication or formulated for intravitreal use.

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

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 DME indication. The PBAC requested the Department investigate these issues on its behalf.

7. Clinical Trials

The re-submission presented two head-to-head randomised trials comparing ranibizumab to laser photocoagulation, as both monotherapy and mixed treatment (RESTORE and DRCR.net). The PBAC noted that the same trials were presented in the March 2013 submission. 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
Trial 2301 (RESTORE)	**Internal study report title:** A randomized, double-masked, multi-centre, laser-controlled Phase III study assessing the efficacy and safety of ranibizumab (intravitreal injections) as adjunctive and mono-therapy in patients with visual impairment due to diabetic macular oedema. The study was conducted between May 2008 and January 2010. Mitchell, Paul, et al. "The RESTORE Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular oedema." *Ophthalmology* 2011; 118(4):615-25.
RESTORE 24 month extension study	**Internal study report title:** An open label, multicentre, 24-month extension study to evaluate the safety of ranibizumab as symptomatic treatment for visual impairment due to diabetic macular oedema in patients who have completed the RESTORE trial. The study was conducted between June 2009 and January 2012.
NCT0044503 (DRCR.net Protocol I)	Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, et al. "Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular oedema." *Ophthalmology* 2010; 117(6):1064-77. Elman MJ, Bressler NM, Qin H, et al. "Expanded 2-Year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular oedema." *Ophthalmology* 2011; 118(4):609-14.

8. Results of Trials

As in the previous submission, the PBAC noted that, within the RESTORE trial, patients who received ranibizumab without or with active laser, achieved, on average, a further 6.2 letters (95% CI: 3.6, 8.7) or 5.4 letters (95% CI: 2.4, 8.4) gained in best-corrected visual accuracy (BCVA) in the treated eye compared to patients who received laser with sham injections. Similarly, within the DRCR.net trial, patients who received ranibizumab with deferred or prompt laser, achieved, on average, a further 6.0 letters (95% CI: 3.4, 8.6) or 5.8 letters (95% CI: 3.2, 8.5) gained in BCVA in the treated eye compared to patients who received prompt laser with sham injections.

The PBAC recalled that it had previously questioned the clinical importance of a five letter gain in BCVA in the treated eye, which is below the ten letter gain required to achieve clinically significant improvement in vision-relation quality of life.

The PBAC noted that the re-submission provided additional discussion to justify the clinical relevance of an improvement of 5-6 letters. First, the RESTORE trial included patients with

relatively good vision (78-39 BCVA letters) who might experience a "ceiling effect". Second, other trials that included patients with poorer eyesight showed larger BCVA letter gains. Lastly, laser photocoagulation causes deleterious long-term effects on the retina even though the mechanism of action is unknown, as acknowledged by the re-submission.

The PBAC agreed with the ESC that these arguments were not grounded in the clinical evidence comparing ranibizumab and laser treatment. The PBAC remained concerned about the clinical importance of a 5-6 letter improvement in BCVA in the treated eye. The PBAC recalled its finding in its consideration of the March 2013 submission that "an increase in 5 letters or more might represent a clinically meaningful difference for some patients in the treatment of DME". The PBAC further clarified that the overall clinical meaningfulness of an improvement of 5 or more letters in the treated eye will depend on the baseline VA of the patient in both eyes and on the subsequent overall VA during and after treatment. Those patients with well-preserved vision at baseline may experience a less clinically meaningful outcome than those patients with poorer vision at baseline.

Overall, the PBAC accepted that ranibizumab is an effective treatment for visual impairment due to DME, but remained concerned about the extent of clinically relevant improvement in overall BCVA in patients with better visual acuity at baseline.

The PBAC noted the additional evidence provided in the re-submission in relation to comparative harms. The Cochrane review identified in the re-submission provided an analysis on the risk of thromboembolic events (RR=0.85; 95% CI: 0.56, 1.28) and deaths (RR=0.95; 95% CI: 0.52, 1.74) for patients receiving anti-VEGF treatment versus control. The re-submission concluded that the results showed no elevated pooled risk of either events overall.

However, the PBAC noted the results of the IVAN study (IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. "Ranibizumab Versus Bevacizumab to Treat Neovascular Age-Related Macular Degeneration: One-Year Findings From the IVAN Randomized Trial." Ophthalmology 2012;119:1399-411) which compared bevacizumab and ranibizumab in patients with age-related macular degeneration, found that fewer patients in the bevacizumab group experienced arteriothrombotic events or heart failure compared with the ranibizumab group (0.7% vs 2.9%; OR=0.23; 95% CI: 0.05, 1.07; *P*=0.03). The PBAC also noted signals for cardiovascular adverse events associated with ranibizumab in the long-term follow-up of the RISE and RIDE study.

No additional data were presented in the re-submission to address the PBAC's concern that conjunctival haemorrhage rates were higher in both RESTORE and DRCR.net trials for ranibizumab, with or without laser, than laser alone. In the RESTORE trial, 7% and 7.5% of patients in the ranibizumab and ranibizumab + laser, respectively, had conjunctival haemorrhage, compared to 0% for the laser arm. Within the DRCR.net trial, ranibizumab + (prompt and deferred) laser treatment compared to prompt laser treatment alone, was associated with a statistically significantly increased risk of conjunctival haemorrhage (deferred laser RR= 9.35; 95% CI: 4.29, 20.38; prompt laser RR= 6.94; 95% CI: 3.12, 15.43).

The PBAC agreed with the ESC advice that, in the event of a positive recommendation to extend the listing of ranibizumab, the results of any risk management plan developed with the TGA as part of the registration process should be provided to the Committee.

A summary of the comparative benefits and harms for ranibizumab versus laser treatment (plus sham injection) is presented in the table below.

Summary of comparative benefits and harms for ranibizumab: comparator = laser treatment (+sham injection)

Outcome	Number of participants (studies) Ranibizumab vs. laser	Relative risk: Ranibizumab vs. laser	Laser: event rate per 100 patients (12 month)	Ranibizumab: event rate per 100 patients (12 month)	Risk difference
Benefits					
≥10 letters gain (from baseline at 12 month)					
RESTORE	115 vs.110	2.42 (1.47; 3.98)	16	37	22% (11%; 33%
DRCR.net	188 vs. 293	1.69 (1.33; 2.15)	28	47	23% (14%; 32%)
≥10 letters loss (from baseline at 12 month)					
RESTORE	115 vs.110	0.27 (0.09; 0.81)	13	4	-9% (-16%; -1%)
DRCR.net	188 vs. 293	0.24 (0.10; 0.56)	13	3	-10% (-15%; -5%)
Harms					
Eye pain					
RESTORE	115 vs.110	1.04 (0.48; 2.27)	10	10	0.4% (-7%; 8%)
DRCR.net	188 vs. 293	1.17 (0.71; 1.92)	11	13	2% (-4%; 8%)
Conjunctival haemorrhage					
RESTORE	115 vs.110	16.3* (0.95; 278)	0	7	7%* (2%; 12%)
DRCR.net	188 vs. 293	9.35 (4.29; 20.38)	4	22	36% (29%; 43%)
Visual impairment					
RESTORE	115 vs.110	6.70* (0.35; 128)	0	3	2%* (0%; 6%)
DRCR.net	188 vs. 293	2.34 (0.67; 8.18)	2	3	2% (-1%; 5%)

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

- Approximately 22 patients would achieve a gain of at least 10 letters in visual acuity (from baseline at 12 months);
- Approximately 9 fewer patients would experience a loss of at least 10 letters in visual acuity (from baseline at 12 months);
- Between 1 and 2 patients would experience eye pain;
- Between 7 and 36 patients would experience conjunctival haemorrhage; and
- 2 patients would experience visual impairment.

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 described ranibizumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over laser photocoagulation.

The PBAC recalled that it had previously considered that in a single treated eye in each patient, ranibizumab was probably superior to laser photocoagulation if it is accepted that a difference of 5 letters is clinically important. However, the re-submission did not provide additional evidence to support the clinical importance of this improvement in overall BCVA.

10. Economic Analysis

The re-submission presented an updated cost-utility analysis based on superiority for comparative benefit and equivalence in terms of comparative safety. The base case ICER per quality adjusted life year (QALY) gained was in the range of $15,000-$45,000 (compared with between $45,000-$75,000 in the previous submission). The base case ICER was revised during the evaluation to include updated MBS fees and discounted laser costs.

The PBAC noted that the reduction in the ICER was largely driven by a decrease in the price of ranibizumab, the change in model structure (from 8 to 4 health states) and updated transition probabilities and utility values.

The PBAC recalled its previous concerns regarding the translation between trial-based VA differences as measured in treated eyes and modelled impacts on utility for patients overall (which will depend on 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 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 and health states of overall VA, which would provide a more plausible basis for the transformation to utilities.

The PBAC also agreed with the ESC that the base case ICER was likely to be underestimated for the following additional reasons:

- ranibizumab treatment does not continue beyond three years, which is inconsistent with the proposed restriction (no stopping rule) and the financial estimates (high impact);
- there is no consideration of ranibizumab treatment of two eyes in part of the population even though a proportion of patients will require treatment in the second eye (medium-high impact);
- the model duration of 15 years is not well justified, given the short trial and the assumption of no treatment beyond year 3 (medium impact); and
- the assumption that ranibizumab will be used as monotherapy, rather than combined with laser therapy (small impact as only some patients may receive combination therapy).

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 determine an appropriate basis to recommend the listing of ranibizumab with reference to bevacizumab without this information.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated that the likely number of patients to be treated with ranibizumab is less than 10, 000 in Year 5 of listing. The PBAC noted that the estimates were higher than in the previous submission due to a higher estimated prevalence of diabetes in the Australian population. The net cost to the PBS was estimated to be in the range of $10-30 million in Year 5 of listing, with a net cost in the first five years of listing in the range of $60-100 million.

The PBAC agreed with the Drug Utilisation Sub-Committee (DUSC) that use beyond the requested restriction was likely, as interpretation of a response may be higher in clinical practice than in the RESTORE trial, and treatment is likely to be continued in patients with small improvements in vision who would have been classified as non-responders in the RESTORE trial, especially since the restriction does not define response nor mandate cessation of treatment according to response.

The PBAC also agreed with the DUSC that diabetic retinopathy is a chronic disease, and the prevalence of diabetes is growing. Patients who commence treatment with ranibizumab are likely to continue in future years and the vast majority will require bilateral treatment. The impact of this is that the pool of treated patients and utilisation of ranibizumab will expand quickly over time, as illustrated by the increase in the predicted number of injections and cost between the first and fifth year of listing.

The PBAC noted the sponsor's interest in entering into a Risk Sharing Arrangement to provide the Commonwealth with certainty of the cost-effectiveness of ranibizumab for DME treatment. The Committee noted that no specific details of a RSA were provided in the re-submission.

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 DME 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 March 2013 and November 2013, that bevacizumab is currently widely used for treatment of DME.

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 DME 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 DME. However, The PBAC remained concerned regarding the extent of clinically relevant improvement in BCVA in patients with better visual acuity at baseline.

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 diabetic macular oedema but firmly believes that bevacizumab is not an appropriate comparator.