

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Ranibizumab, solution for intravitreal injection, 2.3 mg in 0.23 mL, Lucentis<sup>®</sup>

**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd

**Date of PBAC Consideration:** March 2013

### **1. Purpose of Application**

The submission requested an extension to the current Authority required listing to include treatment, by an ophthalmologist, of a patient with visual impairment due to diabetic macular oedema.

### **2. Background**

Ranibizumab had not previously been considered by PBAC as a treatment option for visual impairment due to diabetic macular oedema.

At its March 2007 meeting, the PBAC considered ranibizumab for treatment of subfoveal choroidal neovascularisation related to age-related macular degeneration (AMD). The PBAC recommended listing on the basis of an ICER of between \$15,000 - \$45,000 for 15 injections in one patient-eye. In March 2012 the PBAC considered additional trial data and confirmed the ICER recommended in March 2007 remained acceptable.

At its November 2012 meeting, the PBAC considered ranibizumab for branch and central retinal vein occlusion. The PBAC rejected the submission on the basis of high and uncertain cost effectiveness.

### **3. Registration Status**

Ranibizumab was approved by the TGA in August 2011 for treatment of visual impairment due to diabetic macular oedema (DME).

### **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.

#### **Authority required**

Continuing treatment by an ophthalmologist, of visual impairment due to diabetic macular oedema, where the patient has previously been granted an authority prescription.

The PBAC noted that proposed restriction wording was broad. It did not define visual impairment; lacked objective clinical indicators; did not include continuation, stopping or recommencing criteria; and did not specify monotherapy.

Of particular concern was that the restriction did not specify whether ranibizumab should be used as first-line therapy, although the submission assumed that it would be.

### **5. Clinical Place for the Proposed Therapy**

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

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

*For PBAC's view, see Recommendation & Reasons.*

## 6. Comparator

The submission nominated laser treatment as the main comparator.

*For PBAC's view, see Recommendation & Reasons.*

## 7. Clinical Trials

The submission presented two clinical trials: RESTORE and the DRCR.net trial.

The RESTORE trial compared three treatment options: ranibizumab monotherapy, laser monotherapy, and ranibizumab + laser in a total of 345 patients with visual impairment due to diabetic macular oedema. The double blind phase of the trial was 12 months, with an open label follow-up period of an additional two years (RESTORE- 24 month extension study), in which all patients received ranibizumab when required. The submission reported that 19-25% of the patients in each treatment group did not require any ranibizumab during the extension phase. Adult patients were recruited on the basis best-corrected visual acuity (BCVA) score was between 78 and 39.

Patients were recruited into the RESTORE trial with Type 1 or Type 2 diabetes mellitus with HbA1c $\leq$ 10% at screening. In addition, around 83% of patients had evidence of bilateral diabetic macular oedema but only 22% would have been eligible for bilateral treatment because their vision was not impaired in the other eye. Finally, 35% of patients (including 29% of bilateral patients) received treatment in their better-seeing eye contrary to the protocol that required the worse-seeing eye to be treated.

The DRCR.net trial compared four treatment options: prompt laser; ranibizumab + prompt laser; ranibizumab + deferred laser; and 4 mg triamcinolone + prompt laser in a total of 691 participants. In the DRCR.net trial, 854 eyes were randomised. For patients with two eligible study eyes, the right eye was assigned randomly to one of the four treatment groups. If the right eye was assigned to any intervention, then the left eye was assigned to sham injection + laser treatment. If the right eye was assigned to sham injection + laser, then the left eye was randomly assigned to any of the three remaining intervention groups.

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

<b>Trial ID/ First author</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Direct randomised trials</b>		
RESTORE (Trial 2301) Mitchell, Paul, et al.	"The RESTORE Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema:	Ophthalmology 2011; 118(4):615-625
DRCR.net Elman MJ, et al.	Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema.	Ophthalmology 2010; 117(6):1064-77

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Elman MJ, et al.	Expanded 2-Year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema.	Ophthalmology 2011; 119 (4):789-801

## 8. Results of Trials

The submission presented the clinical relevant outcome of mean change in best-corrected visual acuity (BCVA) (score between 1-100) of the treated eye from baseline to 12 months as the primary outcome for DRCR.net trial and as the secondary outcome for RESTORE trial. Results are presented in the table below.

### Results of BCVA mean change (letters) from baseline at month 12 in the RESTORE and DRCR.net trials

Trial ID	Ranibizumab Sham laser	Ranibizumab Active laser	Sham injection Active laser
<b>RESTORE<sup>a</sup>, N</b>	115	118	110
Baseline, mean (SD)	64.7 (10.1)	63.4 (10.0)	62.6 (11.0)
At month 12	71.5 (11.8)	69.7 (14.2)	63.4 (14.0)
Mean change (letters) from baseline at month 12 (95% CI)	6.8 (5.3, 8.3)	6.4 (4.2, 8.5)	0.9 (-1.3, 3.0)
Comparison vs. Laser, difference in LS means (95% CI)	<b>6.2 (3.6, 8.7)</b>	<b>5.4 (2.4, 8.4)</b>	
<b>DRCR.net<sup>b</sup> 12 month</b>	<b>Ranibizumab + deferred laser</b>	<b>Ranibizumab + prompt laser</b>	<b>Sham + prompt laser</b>
<b>N eyes</b>	188	187	293
Baseline, median (25/75 <sup>th</sup> )	66 (58, 72)	66 (55, 72)	65 (56, 73)
Change from baseline at month 12	9 (12)	9 (11)	3 (13)
Comparison vs. prompt Laser, difference in mean change (95% CI)	<b>6.0 (3.4, 8.6)</b>	<b>5.8 (3.2, 8.5)</b>	

**Bold** = statistically significant; CI = confidence interval; LS = least-squares

<sup>a</sup> = Within the RESTORE trial, laser was administered contemporaneously to intravitreal injection.

<sup>b</sup> = Within the DRCR.net trial, prompt laser was administered 1 week (3-10 days) after intravitreal injection and deferred laser was not given until 6 months visit.

In the RESTORE trial, patients who received ranibizumab with either sham or 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) gain in BCVA of the treated eye compared to patients who received laser and sham injections. The PBAC noted that this was below the previously considered 10 letters gain required to achieve a clinically significant improvement in vision-related quality of life.

In the DRCR.net trial, patients who received ranibizumab and prompt laser achieved 5.8 letters gain (95% CI: 3.2, 8.5) in BCVA of the treated eye compared to patients who received laser and sham injections only. Patients who received ranibizumab and deferred laser achieved 6 letters (95% CI: 3.4, 8.6) gain in BCVA of the treated eye compared to patients who received prompt laser and sham injections only.

A secondary outcome measure in the RESTORE and DRCR.net trials was the proportion of eyes (%) with either a  $\geq 10$  letter improvement or  $\geq 10$  letter worsening in BCVA of the treated eye from baseline to month 12. The PBAC noted that in the RESTORE trial, at month 12, 43.2% of patients in the ranibizumab + laser arm gained 10 letters or more compared to 37.4% in the ranibizumab arm and 15.5% in the laser arm. The PBAC

considered that, whilst an improvement of 10 letters may represent a clinically important result, the relative risk difference shows the majority of people did not achieve an improvement of 10 letters.

In RESTORE, serious adverse events were higher (22.6%) in the ranibizumab plus sham laser than ranibizumab plus active laser (16.7%) and sham injection plus active laser (15.5%), with a relative risk of 1.46 (95% CI: 0.84, 2.54) for ranibizumab versus sham injection plus active laser. In addition, 42.6% of the patients in the ranibizumab arm reported at least one ocular adverse event compared to 39.1% of the patients in the laser arm. Also, 24.3% of the patients in the ranibizumab arm reported at least one adverse event related to ranibizumab and/or ocular injection compared to 18.2% of the patients in the laser arm. Finally, adverse events led to 6.1% of the patients discontinuing in the ranibizumab arm compared to 5.5% of the patients in the laser arm.

In the DRCR.net trial, the mean number of systemic adverse events reported per participant over two years with one study eye was 3/130 (2.3%) in the sham group, and 3/263 (1.1%) in the two ranibizumab groups combined.

Based on the RESTORE-24 month extension study, eye pain was the most frequent ocular adverse event reported (suspected to be related to ocular injection) across treatment groups in patients who received ranibizumab injections during the extension.

*For PBAC's view, see Recommendation & Reasons.*

## **9. Clinical Claim**

The submission claimed that ranibizumab was superior in terms of comparative effectiveness and equivalent in terms of comparative safety over laser photocoagulation.

*For PBAC's view, see Recommendation and Reasons.*

## **10. Economic Analysis**

The submission presented a cost utility analysis based on a claim of superior comparative benefit and equivalent comparative safety. The model used was a nine-state Markov model with two alternative pathways. The model was based on the RESTORE trial 12-month data and then extrapolated for 15 years. The base case ICER was between \$45,000 and \$75,000 per quality adjusted life year (QALY) gained. The ICER was reduced to between \$15,000 and \$45,000 following a price reduction offered in the submission's pre-PBAC response.

*For PBAC's view, see Recommendation & Reasons.*

## **11. Estimated PBS Usage and Financial Implications**

The submission estimated the net PBS cost over 5 years to be between \$30 - \$60 million, based on the revised price offer made in the submission's pre-PBAC response. The PBAC considered the expenditure might be underestimated due to uncertainty in the number of patients likely to be treated. The PBAC was not confident that all use would be cost effective, particularly if the proportion of use in second eyes exceeded expectations.

## **12. Recommendation and Reasons**

The PBAC rejected the submission on the basis of uncertainty about the ICER, uncertainty about comparative long-term safety, and lack of clarity in the extent of benefit measured as an average difference of 5 letters for the treated eye.

The PBAC noted that at the Sponsor's hearing, the specialist's view was that ranibizumab would be a physician's choice for first line therapy as monotherapy and that optical coherence tomography and visual acuity measures would be used in monitoring treatment.

The PBAC considered that laser treatment is the appropriate comparator when ranibizumab is used as monotherapy. The PBAC considered that bevacizumab is also a relevant comparator because it is currently widely used for the treatment of diabetic macular oedema, as confirmed by the clinician during the Sponsor's hearing. However, bevacizumab is not TGA approved for this indication and is not formulated for intravitreal use. Further, the cost-effectiveness of bevacizumab for diabetic macular oedema is not known. As it advised in its November 2012 consideration of ranibizumab for treatment of retinal vein occlusion, the PBAC considered it would be necessary to establish the evidence base for, and cost-effectiveness of, bevacizumab as the comparator in diabetic macular oedema, then establish the incremental cost-effectiveness of ranibizumab against it.

The PBAC considered the applicability of the trial population results to the likely eligible PBS population to be uncertain. The extent of benefit may be less in the Australian PBS population than that measured in the clinical trials. The PBAC was concerned that the clinical difference in visual acuity was smaller than that accepted in other conditions. The PBAC was somewhat reassured by the Sponsor's hearing that there is a benefit to patients with DME in a small increase in visual acuity, but remained concerned about the frequency and duration of treatment required and the extent to which patients would require treatment in their second eye.

The PBAC noted the Sponsor's comments in the Pre-Sub-Committee Response and the hearing; compared to the age-related macular degeneration (AMD) trials in the March 2007 PBAC submission, the DME patients had higher baseline visual acuity and therefore the relative improvement may be less as visual acuity cannot be higher than 100. The PBAC recalled it had previously accepted that an improvement in visual acuity of 10 letters represented a clinically important result. The PBAC was uncertain as to whether an improvement in visual acuity of 5-6 letters could also be considered clinically important. The PBAC agreed that an increase of 5 letters or more might represent a clinically meaningful difference for some patients in treatment of DME, but the clinical importance will also depend on the baseline visual acuity of each eye.

The PBAC noted that, in the RESTORE trial, there was no significant difference in quality of life as measured by EQ-5D, but a difference was suggested when the Visual Function Questionnaire (VQF-25) was applied. At 12-months, excellent to good eye sight was reported in 46% in the ranibizumab arm and 50% in the ranibizumab plus laser arm compared to 25% in the laser alone arm.

Regarding the clinical claim, the PBAC accepted that, in a single treated eye in each patient, ranibizumab is probably superior to laser photocoagulation if it is accepted that a difference of 5 letters is clinically important.

The PBAC noted that patients with diabetes may present with oedema in their second eye following treatment in the first eye. In a small proportion of patients this will be within the time that the first eye is being treated. These people would be eligible for treatment (under the proposed restrictions). The PBAC noted that potential benefit in this scenario was difficult to determine, as the trials mostly assessed one eye per patient only and the trials' criteria for the choice of the treated eye may be different to that in usual practice.

The PBAC considered that the trial results did not support a claim of similar comparative safety between ranibizumab and laser therapy. The statistical power to detect differences between ranibizumab and laser is poor. In addition, rates of conjunctival haemorrhage, were higher in the DRCR.net trial for ranibizumab with laser than laser alone.

The PBAC considered that the provided economic model type was suitable but noted that the multiple health states, derivation of transition probabilities and derivation of utilities were problematic and favoured ranibizumab. The estimated transition probabilities have poor reliability as they are based on small samples of subgroups in the RESTORE trial. The multiple health states, while representing health states that occurred in the trials, have uncertain clinical relevance in terms of distinguishing differences in quality of life. The method for deriving utilities from the EQ-5D results resulted in low correlation values and the derived utilities are different from other sources of utilities measuring the impact of loss of vision in diabetes.

The PBAC remained concerned that the estimated ICER may not reflect the actual benefit of treatment because it is based on evidence related to treatment of one eye (usually the poorer seeing eye) with the relationships between visual acuity and other outcomes (e.g., quality of life, falls) based only on the visual acuity in the worse eye without acknowledging that these relationships are also affected by the visual acuity of the other eye. The PBAC considered that once these relationships are corrected to better reflect the consequences for the overall patient rather than just for the treated eye, the ICER will increase.

The PBAC noted that the sponsor had proposed a risk sharing arrangement. This would be useful in addressing the issue of total cost, but would not address the issues associated with the model addressing the issue of cost effectiveness. In order for the PBAC to consider any changes proposed to the model, a major re-submission would be required.

The PBAC noted the consumer comments received in relation to the submission.

The PBAC noted that the submission meets the criteria for an Independent Review.

***Recommendation:***

Rejected

**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 acknowledges the views of the PBAC. Novartis is committed to addressing the issues of concern so that patients with visual impairment due to diabetic macular oedema may access ranibizumab.