PUBLIC SUMMARY DOCUMENT

Product: Ranibizumab, solution for intravitreal injection, 3.0 mg/0.3 mL, Lucentis®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The submission sought a Section 85 Authority Required listing for neovascular age-related macular degeneration (AMD).

2. Background

The PBAC had not previously considered this drug.

3. Registration Status

Lucentis was registered by the TGA on 27 February 2007 for the treatment of neovascular ("wet") age-related macular degeneration (AMD). Lucentis 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month.

4. Listing Requested and PBAC's View

The following wording of the restriction was proposed for the "prn" (when required) dosing regimen:

Initial treatment
Active neovascular (wet) age-related macular degeneration. The eye(s) being treated must be specified in the authority application.
Continuation treatment
Neovascular (wet) age-related macular degeneration (AMD), in patients previously treated with ranibizumab with evidence of continued disease activity as defined by a loss of 5 letters of visual acuity (ETDRS or one Snellen line equivalent) and/or evidence of leakage of fluid, haemorrhage or lesion growth.
The visual acuity loss must be relative to the best visual acuity achieved on ranibizumab therapy. The most recent best visual acuity measure must be within the past 12 months.
Re-treatment should not be given more frequently than once every month.

The following wording of the restriction was proposed for the "monthly" dosing regimen:

Active neovascular (wet) age-related macular degeneration. The eye(s) being treated must be specified in the authority application.

See Recommendations and Reasons for PBAC's view

5. Clinical Place for the Proposed Therapy

AMD is a progressive disease of the retina that results in loss of central vision, leaving only peripheral vision intact. The exudative or neovascular (wet) form of AMD involves the breaching of a functional retinal barrier and growth of abnormal blood vessels into the central part of the retina. Ranibizumab is a new treatment for exudative macular degeneration.

6. Comparator

The submission nominated two comparators. Consistent with the current available reimbursed treatment for subfoveal neovascular AMD; photodynamic therapy with verteporfin (PDT-V) is the main comparator for ranibizumab when used to treat patients with predominantly classic lesions and standard care is the main comparator for ranibizumab when used to treat patients with occult or minimally classic lesions.

7. Clinical Trials

The submission presented the following three randomised comparative trials:

- ANCHOR trial, comparing ranibizumab (administered monthly) with PDT-V in patients with predominantly classic lesions;
- MARINA trial, comparing ranibizumab (administered monthly) with placebo in patients with minimally classic and occult CNV lesions; and
- PIER trial, comparing ranibizumab (administered for three consecutive months, then administered every three months) with placebo in patients with predominantly and minimally classic, and occult CNV lesions.

Two of these studies had been published at the time of the submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
ANCHOR/Brown	Ranibizumab vs verteporfin for neovascular age-related macular degeneration (report of trial results at 12 months)	Brown et al. N Engl J Med 2006;355:1432-44
MARINA/Rosenfeld	Ranibizumab for neovascular age-related macular degeneration (report of trial results at 12 and 24 months)	Rosenfeld et al. N Engl J Med 2006; 355:1419-31

8. Results of Trials

The results of the key trials are summarised in the tables below. Some trial results/numbers in this PSD are taken from cited publications and may vary slightly from numbers considered by the PBAC which were taken from the sponsor's internal reports.

Proportion of patients losing fewer than 15 letters in visual acuity compared with baseline at 12 and 24 months, based on assessment at a starting test distance of 2 metres

Trial	Sham injection	PDT-V	RAN 0.3mg	RAN 0.5mg	ARD[§] (95% CI)	
Results at 12 months						
ANCHOR[a]		92/143 (64.3%)	132/140 (94.3%)	134/139 (96.4%)	RAN 0.3 vs PDT-V **30.1% (21.8%, 38.5%)**	RAN 0.5 vs PDT-V **31.5% (24.5%, 40.6%)**
MARINA[a]	148/238 (62.2%)		225/238 (94.5%)	227/240 (94.6%)	RAN 0.3 vs Sham **31.9% (25.4%, 38.5%)**	RAN 0.5 vs Sham **32.0% (25.5%, 38.6%)**
PIER	NR		NR	NR	NR	NR

Results at 24 months						
MARINA	126/238 (52.9%)		219/238 (92%)	216/240 (90%)	RAN 0.3 vs Sham **38.7% (31.7%, 45.7%)**	RAN 0.5 vs Sham **36.6% (29.4%, 43.7%)**

* From the Cochran chi square tests adjusted for the strata

§ Weighted estimates adjusting for the strata by using Cochran-Mantel-Haenszel weights

[a] primary outcome of the trials

The data suggested that ranibizumab reduced visual loss at 12 and 24 months in monthly dosing regimen compared with both PDT-V and with placebo. Ranibizumab had a similar effect in predominantly classic CNV-AMD (at 12 months) and in combined minimally classic and occult CNV-AMD (at 12 and 24 months). The 0.3 mg and 0.5 mg doses appeared to be similar in efficacy at the 24-month timepoint.

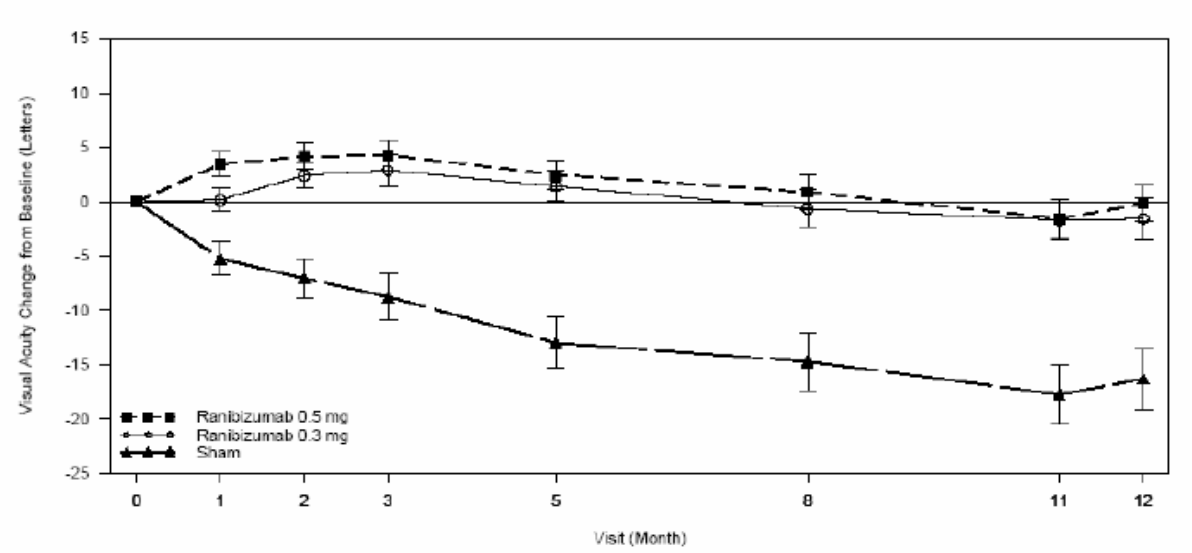
Proportion of patients gaining ≥15 letters in visual acuity compared with baseline at 12 and 24 months, based on assessment at a starting test distance of 2 metres

Trial	Sham injection	PDT-V	RAN 0.3mg	RAN 0.5mg	ARD[§] (95% CI)	
12 months						
ANCHOR		8/143 (5.6%)	50/140 (35.7%)	56/140 (40.3%)	RAN 0.3 vs PDT-V **30.1% (21.4%, 38.8%)**	RAN 0.5 vs PDT-V **34.9% (25.9%, 43.8%)**
MARINA	11/238 (5.0 %)		59/238 (24.8%)	81/240 (33.8%)	RAN 0.3 vs Sham **19.9% (13.8%, 25.9%)**	RAN 0.5 vs Sham **28.7% (22.3%, 35.0%)**
PIER	NR		NR	NR	NR	NR
24 months						
MARINA	9/238 (3.8%)		62/238 (26.1%)	80/240 (33.3%)	RAN 0.3 vs Sham **21.9% (16.0%, 27.9%)**	RAN 0.5 vs Sham **29.2% (22.9%, 35.4%)**

The data above suggested that monthly ranibizumab led to improvements in vision in about 20-30% of patients with all types of CNV-AMD at 12 and 24 months compared with PDT-V and with PBO. The 0.5 mg dose generally appeared to be more effective than the 0.3 mg dose.

Although statistically significant differences were observed in proportions of patients gaining ≥15 letters in visual acuity between ranibizumab-treated and control subjects in the trials where ranibizumab was administered monthly, there was no significant difference in the proportion of patients gaining ≥15 letters in visual acuity when ranibizumab was administered in three-monthly doses followed by administration every three months compared with placebo in patients with any CNV lesion type (results from PIER). This suggested that treatment on a monthly basis may be associated with improved outcomes compared with treatment every 3 months.

PIER Mean Change from Baseline over Time in Visual Acuity



Statistically significant differences in effectiveness were generally observed in the results from the MARINA trial between patients treated with ranibizumab 0.3 mg compared with patients treated with ranibizumab 0.5 mg, with results favouring ranibizumab 0.5 mg.

Although the same trend was observed in the other trials, differences between doses did not reach statistical significance.

In relation to the comparison of monthly ranibizumab versus PDT-V (ANCHOR trial), the incidence of ocular adverse events related to the study drug was higher in the ranibizumab treatment arms compared with the PDT-V arm. The ocular adverse events occurring more frequently in the ranibizumab-treated arms than PDT-V arm include conjunctival haemorrhage, increased intraocular pressure, eye pain, iritis, vitritis and vitreous floaters.

9. Clinical Claim

Ranibizumab has significant advantages in effectiveness over PDT-V but is associated with greater toxicity in patients with predominantly classic CNV lesions in patients with visual acuity ≥20/200; ranibizumab has significant advantages in effectiveness over placebo but is associated with greater toxicity in patients with minimally classic and occult CNV lesions. The PBAC considered the claim reasonable.

10. Economic Analysis

The submission presented a series of preliminary (trial-based) economic evaluations based on the results from the ANCHOR, MARINA, and PIER trials. The choice of the cost-effectiveness approach was valid. The resources included were drug costs, costs of administering ranibizumab by intravitreal injection, costs of administering PDT-V (infusing verteporfin and subsequent laser irradiation of the macula), and costs of monitoring (follow-up consultation, diagnostic tests and ophthalmic imaging). The overall comparative costs and outcomes for each alternative and the incremental costs and outcomes are summarised below.

Based on the results of the ANCHOR trial the incremental cost/extra patient losing

< 15 letters at the 0.5 mg ranibizumab dose over 12 months was between $45,000 and $75,000.

Based on the results of the MARINA trial the incremental cost/extra patient losing < 15 letters over 24 months was between $105,000 and $200,000.

Based on the PIER trial the incremental cost/extra patients losing < 15 letters over 12 months was between $15,000 and $45,000.

The submission presented a series of modelled economic evaluations. The choice of the cost-utility approach was appropriate. The PBAC noted the 5-year model incorporated the effects of a risk sharing agreement.

In patients with predominately classic CNV lesion the incremental cost-effectiveness ratio/extra QALY gained for ranibizumab 0.5 mg monthly was between $15,000 and $45,000.

In patients with predominately classic CNV lesions the incremental cost-effectiveness ratio/extra QALY gained for ranibizumab 0.5 mg monthly for 3 months then every 2 months was between $15,000 and $45,000.

In patients with minimally classic CNV lesions the incremental cost/extra QALY gained for ranibizumab 0.5 mg monthly was between $$45,000 and $75,000.

In patients with minimally classic CNV lesions the incremental cost/extra QALY gained for ranibizumab 0.5 monthly for 3 months then every 2 months was between $105,000 and $200,000.

In patients with occult CNV lesions, the incremental cost/extra QALY gained for ranibizumab 0.5 mg monthly was between $45,000 and $75,000.

In patients with occult CNV lesions the incremental cost/extra QALY gained for ranibizumab 0.5 monthly for 3 months then every 2 months was between $105,000 and $200,000.

The weighted average cost-effectiveness of ranibizumab 0.5 monthly for all lesions types was between $15,000 and $45,000.

The weighted average cost-effectiveness of ranibizumab 0.5 monthly for 3 months then every 2 months $45,000 and $75,000.

11. Estimated PBS Usage and Financial Implications

The predicted net cost to government was estimated to be > $100 million per year.

12. Recommendation and Reasons

The PBAC recommended listing for the treatment of subfoveal choroidal neovascularisation (CNV) due to age related macular degeneration on a cost-effectiveness basis against verteporfin with PDT in predominantly classic disease, and against placebo in minimally

classic or occult disease. Listing was recommended at the price proposed in the submission on the basis of an average incremental cost per extra quality adjusted life year (QALY) gained across all lesion types of between $15,000 and $45,000 on the basis of the arrangement proposed by the sponsor.

The PBAC did not agree to the sponsor's proposed "prn" (when necessary) dosing regimen, noting that (a) it is not consistent with the TGA recommended dosing regimen and (b) there is currently no direct clinical trial evidence supporting the efficacy of treatment using the regimen proposed and some clinical trial evidence from the PIER trial which suggests it may be associated with worse outcomes than monthly dosing. Of the three key trials submitted in support of listing, two (ANCHOR and MARINA) used a monthly dosing schedule and one (PIER) used a less frequent dosing schedule, albeit different to the sponsor's proposed "prn" schedule. A comparison across the results of the three trials suggests that injections given on a monthly basis may be associated with improved outcomes compared with injections given every 3 months. The PBAC considered it was important that an appropriate Quality Use of Medicines (QUM) program be undertaken to ensure that clinicians are aware of the most effective dosing schedule for ranibizumab.

The PBAC further recommended that prescribing under the PBS be restricted to ophthalmologists as the sole CNV therapy subsidised at any one time.

The PBAC indicated concern about the large amount of wastage and suggested that the sponsor investigate a smaller pack size. The PBAC also indicated concern about the storage of this product and the need to maintain the cold-chain. This issue is of particular concern for the period between dispensing and administration and the PBAC requested the sponsor implement QUM measures to minimise the chance of the cold-chain being interrupted at this point.

Recommendation

RANIBIZUMAB, solution for intravitreal injection, 3.0 mg/0.3 mL,

Authority Required

Initial treatment by an ophthalmologist, as the sole subsidised therapy, of subfoveal choroidal neovascularisation (CNV) due to age related macular degeneration (AMD), as diagnosed by fluorescein angiography.

Authority approvals will be administered by the PBS and Specialised Drugs Branch of Medicare Australia.

The first authority application for each eye must be made in writing, and must include:

a) a completed authority prescription form;
b) a completed Subfoveal Choroidal Neovascularisation (CNV) – PBS Supporting Information Form [www.medicare.gov.au]; and
c) a copy of the fluorescein angiogram.

Written applications for authority to prescribe ranibizumab should be forwarded to:
Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826

GPO Box 9826
HOBART TAS 7001

Alternatively, the first authority application may be faxed to Medicare Australia on (03) 6215 5474 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Medicare Australia will then contact the prescriber by telephone. The original documentation must be posted to the above address after approval has been gained.

Max Quantity: 1
Number of Repeats: 0

Authority Required
Continuing treatment by an ophthalmologist, as the sole subsidised therapy, of subfoveal choroidal neovascularisation (CNV***)*** due to age related macular degeneration (AMD) where the patient has previously been granted an authority prescription for the same eye.

Authority approvals will be administered by the PBS and Specialised Drugs Branch of Medicare Australia. Authority applications for continuing treatment in the same eye may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Max Quantity: 1
Number of Repeats: 1

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 chose not to make a comment.