

Public Summary Document

Product: Anecortave acetate, depot suspension, 15 mg in 0.5 mL, Retaane®
Sponsor: Alcon Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: March 2006

1. Purpose of Application

The submission requested listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment by specialist ophthalmologists of exudative age related macular degeneration (AMD), which meets certain criteria.

2. Background

This drug had not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Anecortave is registered for the treatment of subfoveal choroidal neovascularisation (CNV) due to exudative age-related macular degeneration (AMD) where there is a classic component.

4. Listing Requested and PBAC's View

Restricted benefit

For the treatment of subfoveal choroidal neovascularisation (CNV) due to exudative age-related macular degeneration (AMD), where there is a classic component.

Treatment can only be undertaken by designated trained specialist ophthalmologists.

The PBAC's view was that any restriction would need to be consistent with that recommended for verteporfin, including limiting treatment to predominantly classic AMD lesions. It was noted that the sponsor had no objection to this approach.

5. Clinical Place for the Proposed Therapy

AMD is a leading cause of new blindness in the elderly patient. There are two forms of AMD- atrophic, or dry macular degeneration and exudative or wet, macular degeneration. Dry AMD occurs in 85-90% of patients with macular degeneration. Exudative age-related macular degeneration (AMD) occurs only in 10-15% of patients with AMD. It is usually more severe and causes more vision loss.

Exudative macular degeneration is characterised by choroidal neovascularisation (CNV), or abnormal growth of blood vessels in the choroid membrane beneath the retina near the macula. Vision loss in the disease is as a direct result of leakage and haemorrhage into the sub retinal space near the macular.

Treatment of exudative AMD includes laser photocoagulation, photodynamic therapy, macular translocation, submacular surgery, vitamin supplements, transpupillary thermotherapy, and a variety of drug therapies including anecortave.

6. Comparator

The submission nominated photodynamic therapy with verteporfin as the main comparator in the treatment of predominantly classic lesions, and placebo as the comparator in the treatment of minimally classic subfoveal CNV secondary to age-related macular degeneration. The PBAC agreed with this approach.

7. Clinical Trials

The submission presented a single randomised head-to-head trial comparing anecortave (15 mg/0.5 mL) with photodynamic therapy with verteporfin (6 mg/m² body surface area) in patients with predominantly classic subfoveal CNV secondary to age-related macular degeneration over 24 months. A further two supplementary randomised trials comparing anecortave with placebo were also included. One of these trials compared anecortave monotherapy and placebo; the other trial compared anecortave + PDT (with verteporfin) and placebo + PDT (with verteporfin).

The key head-to-head trial had not been published at the time of submission. Both supplementary trials had been published as follows:

Trial/First author	Protocol/Publication title	Publication citation
C-98-03 Augustin AJ et al	Safety of posterior juxta-scleral depot administration of the angiostatic cortisene anecortave acetate for treatment of subfoveal choroidal neovascularization in patients with age-related macular degeneration.	Graefe's archive for clinical and experimental ophthalmology 2005; 243:9-12.
D'Amico DJ et al	Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve month clinical outcomes.	Ophthalmology 2003; 110:2372-83; discussion 2384-5.
D'Amico DJ et al	Anecortave acetate as monotherapy for the treatment of subfoveal lesions in patients with exudative age-related macular degeneration (AMD): Interim (month 6) analysis of clinical safety and efficacy.	Retina 2003; 23:14-23.
Schmidt-Erfurth U et al	Anecortave acetate for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration.	European Journal of Ophthalmology 2005; 15:482-5.
Regillo CD et al	Safety of anecortave acetate administered as posterior juxtasclear injection in patients with subfoveal choroidal neovascularization.	American Academy of Ophthalmology 2002; 282pp
C-00-07/ Regillo CD et al	Safety of anecortave acetate administered as posterior juxtasclear injection in patients with subfoveal choroidal neovascularization.	American Academy of Ophthalmology 2002; 282pp.

8. Results of Trials

In the key head-to-head trial there was no statistically significant difference in the loss of <3-line visual acuity loss between anecortave and verteporfin (per protocol analysis: -0.04; 95% CI -0.13 to 0.06). The confidence interval around the difference in treatment effect between anecortave and PDT extended beyond the pre-specified non-inferiority criterion of 7.0% for the per protocol and intent to treat (ITT) analyses. However, the submission claimed that a non-inferiority margin of 14% should be acceptable for this trial.

The submission also requested that difficulties in the trial be considered in interpreting the results, particularly poor administration technique and non-attendance within the specified time period.

The supportive trials presented were trials C-98-03 and C-00-07. Trial C-98-03 showed a significant improvement in comparison with placebo in predominantly classic but no difference in minimally classic lesions. Trial C-00-007 compared efficacy and safety of anecortave in combination with verteporfin with verteporfin monotherapy. There was no statistically significant difference between anecortave and placebo when anecortave was used in combination with verteporfin for the primary outcome of mean change in logMAR visual acuity scores at 6 months.

The safety profile of anecortave appeared to be similar to that of verteporfin as the ocular and non-ocular adverse events reported for the two treatments occurred at similar rates. Adverse events occurring at a rate of greater than 1% in either the anecortave or verteporfin groups in the key trial were decreased visual acuity (5.8% vs 2.2%), eye pain (2.7% vs 1.9%), cataract (1.2% vs 1.1%), eye hyperaemia (1.2% vs 0.7%), IOP decrease (1.2% vs 0%) foreign body sensation (0% vs 1.5%). There were no non-ocular adverse events that occurred at a rate of greater than 1.0% in either the anecortave or verteporfin groups.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that anecortave was safe, well tolerated and as effective as photodynamic therapy with verteporfin for the treatment of age-related macular degeneration in patients with classic lesions.

The PBAC did not accept that anecortave is as effective as verteporfin, *see Recommendation and Reasons.*

10. Economic Analysis

The submission undertook a cost minimisation analysis for the preliminary economic evaluation. As the PBAC did not conclude that anecortave was no worse than verteporfin, the rationale for undertaking a cost-minimisation analysis was weak.

The submission did not present an economic model.

11. Estimated PBS Usage and Financial Implications

The total cost to the PBS of listing anecortave was estimated in the submission to be <\$10 million in year 3 of listing. The submission claimed that the PBS listing of anecortave would result in a net saving to the PBS because of less use of verteporfin.

12. Recommendations and Reasons:

The PBAC noted that the supportive evidence from Trial C-98-03 showed a non-significant difference in minimally classic lesions for anecortave in comparison with placebo (the appropriate comparator for this patient group, given that verteporfin was recommended only for predominantly classic lesions). The PBAC agreed that the appropriate comparator in predominantly classic lesions was photodynamic therapy (PDT) with verteporfin, as nominated by the submission. Thus, the PBAC considered that any restriction would need to be consistent with that recommended for verteporfin, ie for predominantly classic AMD lesions only. It was also noted that the sponsor of anecortave had no objection to this approach, including restricting use of anecortave to patients with a baseline visual acuity \geq 6/60 (20/200). The PBAC also noted that there is no evidence from the clinical trials on how many doses of anecortave may continue to be useful, but advice from ophthalmologists was that CNV tends to stabilize after about two years and it becomes clinical judgment about whether continuing treatment might be of value.

The PBAC did not accept the submission's claim that anecortave is no worse than PDT with verteporfin in terms of effectiveness and safety, in the treatment of age-related macular degeneration in patients with predominantly classic lesions. The pre-specified non-inferiority criterion (a confidence interval that does not extend beyond 7.0% inferior) was not satisfied for either the per protocol or ITT analyses comparing anecortave and PDT with verteporfin in the key trial. The PBAC considered that the submission had not adequately justified its argument that a post-hoc non-inferiority margin of 14% should be acceptable for this trial rather than the pre-specified margin of 7%. On the basis of the -4% difference between anecortave and verteporfin, with a confidence interval of -13% to 6%, and a pre-specified non-inferiority criterion that has not been met, the possibility that anecortave is inferior in comparison with verteporfin cannot be excluded.

The PBAC considered that the approach of defining a non-inferiority margin based on the proportion of the difference between active comparator and placebo was inappropriate. On this basis, the non-inferiority margin of 14% was considered arbitrary and the PBAC thus agreed that justification for a post-hoc 14% non-inferiority criterion was weak. The rationale for undertaking a cost-minimisation analysis was also weak.

The PBAC accepted that the issues of reflux could be addressed by adequate training in injection technique and use of the Counter Pressure Device. However, it was noted that the TGA-approved product information for anecortave acetate recommends administration of anecortave acetate "every 6 months (but not to exceed 6 months)". The Committee was not convinced that it would be possible to ensure that all patients are treated at an interval of not more than (but also not less than 6 months) because attendance at the appropriate interval would depend on both patients and providers.

The PBAC thus rejected the submission because of inadequate evidence to support the claim that that anecortave is no worse than PDT with verteporfin, in terms of effectiveness and safety.

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

Alcon is working with the PBAC on options for a possible listing.