PUBLIC SUMMARY DOCUMENT
Product: Aflibercept, solution for intravitreal injection, 40 mg per mL, Eylea®
Sponsor: Bayer Australia Pty Ltd.
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission requested an Authority Required listing for initial and continuing treatment by an ophthalmologist, as sole PBS-subsidised therapy, of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD).

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Aflibercept was TGA registered on 7 March 2012 for the treatment of neovascular (wet) age-related macular degeneration (wet AMD).

4. Listing Requested and PBAC's View

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.

Where a fluorescein angiogram cannot be performed due to a contraindication as listed in the TGA-approved product information, details of the contraindication must be provided. A copy of the report of an alternative method of diagnosis must be included in the application, for example, optical coherence tomography (OCT) or red free photography.

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 aflibercept 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.

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).

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Neovascular (wet) AMD is due to choroidal neovascularisation which involves the growth of new blood vessels from the choroid capillary network into the neural retina, resulting in retinal detachment, subretinal and intraretinal oedema, and scarring. CNV can occur near or under the foveal centra (juxtafoveal or subfoveal respectively), severely reducing visual acuity.

The submission proposed that the place in therapy of aflibercept would be as an alternative anti-VEGF agent for patients with subfoveal CNV, with a reduced frequency of injections and monitoring visits.

6. Comparator

The submission nominated ranibizumab as the main comparator, stating that it is the most frequently prescribed therapy for wet AMD in clinical practice based on a review of PBS prescription volumes dispensed. This comparator was accepted by the PBAC.

7. Clinical Trials

The submission presented two direct randomised comparative trials and one pre-specified pooled analysis of two trials comparing aflibercept with ranibizumab in patients with wet AMD. VIEW 1 and 2 trials are Phase 3 non-inferiority trials of two years duration comparing ranibizumab 0.5 mg every month (R 0.5Q4) with three different treatment options of aflibercept; 0.5 mg every month (AFT 0.5Q4), 2 mg every month (AFT 2Q4) or 2 mg every second month (AFT 2Q8), following three initial monthly injections. The first year of the trial followed a fixed dose regimen and fixed treatment schedule, while the second year continued with the fixed dose regimen but adopted an "as needed" treatment schedule for all treatment arms.

The primary outcome of the two trials was the proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline. The specified non inferiority margin of 10% was determined based on expert clinical advice and a regulatory agreement in 2007.

The submission presented year one data only from the VIEW 1 and 2 trials in the analyses.

These trials had not been published at the time of submission.

8. Results of Trials

The results of vision maintenance comparing aflibercept to ranibizumab across the direct randomised trials showed that both ranibizumab and aflibercept resulted in a high proportion of subjects who maintained vision at week 52. The differences between aflibercept (AFT 2Q8) and ranibizumab (R 0.5Q4) were not statistically significant. The specified non-inferiority criteria was met in all aflibercept treatment arms in the per protocol analysis.

The incidence of severe ocular treatment emergent adverse events (TEAEs) in VIEW 1 between R 0.5Q4 and AFT 2Q8 was significantly lower for AFT 2Q8. However the absolute difference was small and not replicated in VIEW 2.

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

9. Clinical Claim

The submission claimed that 2 mg of aflibercept administered every second month following three initial monthly injections is non-inferior to 0.5 mg of ranibizumab administered monthly in terms of efficacy and safety.

The submission also claimed that less frequent injections required for aflibercept will help to reduce the burden on patients, caregivers, physicians and the healthcare system.

The PBAC considered it was uncertain whether less frequent injections will eventuate with aflibercept treatment compared to ranibizumab treatment. The PBAC noted from the Drug Utilisation Subcommittee's (DUSC) review that ranibizumab is not in fact being administered monthly, and it is therefore unlikely patients treated with aflibercept would receive fewer injections. Currently the average number of injections in the first 12 months of treatment is 7.42. This has been slowly increasing with prescribers becoming more experienced, improved use of diagnostic techniques to improve detection and monitor disease progression and the developing view of these drugs as chronic therapies.

Overall, the PBAC considered the submission's claim (for maintenance of vision) was reasonable, based on the year one results of VIEW-1 and VIEW-2.

However, the PBAC considered that the conclusion that 2 mg aflibercept is non-inferior to 0.5 mg ranibizumab (in terms of maintenance of vision) may also be reasonable. There was no clinical evidence provided that aflibercept would be used in a different way to ranibizumab currently by retinal specialists, i.e. the number of injections per patient per year for each product is likely to be similar.

For PBAC's view, see Recommendations and Reasons

10. Economic Analysis

The submission presented a cost minimisation analysis comparing a treatment frequency using the number of injections as per the Product Information for aflibercept (7 per year) and current practice (based on PBS data analysis for 12-month continuers) for ranibizumab (8.8 per year).

For PBAC's view, see Recommendations and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated in the submission to be less than 10,000 in Year 5. The PBAC considered that the number of patients with CNV-AMD was underestimated and therefore the use of aflibercept is an underestimate.

The submission estimated net cost savings to the PBS.

For PBAC's view, see Recommendations and Reasons

12. Recommendation and Reasons

The PBAC recommended listing aflibercept on the PBS as an Authority Required benefit for treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD) (wet AMD) on a cost-minimisation basis with ranibizumab, with one aflibercept 2 mg injection being equivalent to one ranibizumab 0.5 mg injection.

The PBAC agreed that ranibizumab was the appropriate comparator as it is the most frequently prescribed therapy for wet AMD in clinical practice.

The PBAC noted the key clinical trials, VIEW-1 and VIEW-2, which compared ranibizumab 0.5 mg administered monthly with three dosing protocols of aflibercept (2 mg monthly, 0.5 mg monthly and 2 mg 8-weekly (following three initial monthly injections)). The primary outcome of the trials was the proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if they had lost fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline.

The PBAC noted the submission's claim that the results for ranibizumab from VIEW-1 and VIEW-2 were consistent with those of the ANCHOR and MARINA trials considered by the PBAC in the March 2007 submission for ranibizumab. However no qualitative comparison was provided and the PBAC considered this conclusion was not well supported.

From the results of the pooled analysis of the year one data from VIEW-1 and VIEW-2, the PBAC noted that both ranibizumab and aflibercept resulted in a high proportion of subjects who maintained vision at week 52. The differences between aflibercept 2 mg 8-weekly and ranibizumab 0.5 mg monthly were not statistically significant for VIEW-1 and VIEW-2. However, the PBAC also noted that the non-inferiority criterion for the difference between ranibizumab and aflibercept in the per protocol analysis was met in all aflibercept treatment arms.

The PBAC noted that incidence of treatment emergent adverse events (TEAEs), ocular TEAEs, non-ocular TEAEs and severe ocular TEAEs were similar across all treatment arms in both trials with no significant differences between ranibizumab and aflibercept.

Overall, the PBAC considered the submission's claim that 2 mg aflibercept administered every second month following three initial monthly injections is non-inferior in terms of efficacy and safety to 0.5 mg of ranibizumab administered monthly (for maintenance of vision) was reasonable, based on the year one results of VIEW-1 and VIEW-2. However, in keeping with its recommendation on equi-effective doses in the context of cost-minimisation,

the PBAC also considered that this conclusion could also be reached for 2 mg aflibercept administered monthly based on the same trials.

The PBAC noted that there was no clinical evidence presented in the submission for use of aflibercept in patients who have failed or are unable to continue treatment with ranibizumab and therefore recommended that the restriction should limit use to treatment naïve patients.

The PBAC noted the submission's cost minimisation analysis compares a treatment frequency for ranibizumab of 8.8 injections per year (based on PBS data analysis for 12-month continuers only) with 7 injections per year for aflibercept. The PBAC noted that there is a high degree of uncertainty regarding the number of injections that will be administered in clinical practice for aflibercept. The analysis of utilisation of ranibizumab shows that this market is changing with longer duration of use and more frequent dosing of ranibizumab. The PBAC considered that second year data from VIEW-1 and VIEW-2 (when available in full) would be informative in this regard.

The PBAC noted the DUSC review of ranibizumab also indicated that approximately 20% of patients were receiving bilateral treatment, and considered that the submission's estimate of the number of prescriptions dispensed for aflibercept is likely to be underestimated as it is based on single eye treatment. Therefore, the PBAC considered that the price of aflibercept should be based on an injection: injection basis with ranibizumab and that the number of doses required each year should not be taken into account.

In making this recommendation the PBAC noted the consumer comments on this item.

The PBAC recommended that aflibercept is out of scope for prescribing by nurse practitioners.

Recommendation:
AFLIBERCEPT, solution for intravitreal injection, 40 mg per mL

Restriction: <u>Authority Required</u>
Initial treatment by an ophthalmologist, as the sole PBS subsidised therapy, of subfoveal choroidal neovascularisation (CNV) due to age related macular degeneration (AMD), as diagnosed by fluorescein angiography, in a treatment naïve patient.

Where a fluorescein angiogram cannot be performed due to a contraindication as listed in the TGA-approved product information, details of the contraindication must be provided. A copy of the report of an alternative method of diagnosis must be included in the application, for example, optical coherence tomography (OCT) or red free photography.

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;

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HOBART TAS 7001

Alternatively, the first authority application may be faxed to Medicare Australia on 1300 093 177 (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
Repeats: 2

Restriction: Authority Required
Continuing treatment by an ophthalmologist, as the sole PBS 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).

Note
No applications for increased repeats will be authorised.

Max quantity: 1
Repeats: 2

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

Bayer accepts the PBAC decision and looks forward to making aflibercept available on the PBS. Nonetheless, Bayer is disappointed with the restriction to treatment naïve patients and

will be working constructively with the PBAC to allow access for those patients who have received prior therapy.