Public Summary Document

Product: Aflibercept, injection, 4 mg/0.1 mL (Eylea®)
Sponsor: Bayer Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The major submission sought an extension to the current Authority required listing as the sole PBS-subsidised treatment of a patient with macular oedema secondary to central retinal vein occlusion (CRVO). A coordinated application to the Medical Services Advisory Committee (MSAC) for Medicare Benefits Schedule (MBS) listing of optical coherence tomography (OCT) to measure the central retinal thickness was lodged simultaneously.

The PBAC noted that OCT would be considered at the MSAC meeting of August 2013

2. Background

Aflibercept had not previously been considered by the PBAC as treatment option for macular oedema secondary to CRVO.

In March 2012, 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) on a cost-minimisation basis with ranibizumab, with one aflibercept 2 mg injection being equivalent to one ranibizumab 0.5 mg injection. Listing was effective 1 December 2012.

3. Registration Status

Aflibercept was TGA registered on 19 December 2013 for use in adults for the treatment of macular oedema secondary to CRVO.

Aflibercept is also indicated in adults for the treatment of of neovascular (wet) age-related macular degeneration (wet AMD).

The PBAC noted that the Therapeutic Goods Administration (TGA) regulatory application for aflibercept for the extension of indications to include treatment of macular oedema secondary to central retinal vein occlusion was still pending and that neither a Clinical Evaluation Report nor TGA Delegate's Overview were available to the PBAC at the time of consideration by the PBAC in July 2013.

4. Listing Requested and PBAC's View

Authority required

Initial treatment by an ophthalmologist, as the sole subsidised therapy, for a patient newly diagnosed with macular oedema caused by central retinal vein occlusion (CRVO) who:

a) Has confirmed presence of central retinal thickening on OCT

b) Presence of documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (ETDRS) chart.

Initial treatment with monthly injections for up to 6 months followed by OCT guided treatment.

Authority required

Continuing treatment by an ophthalmologist, as the sole subsidised therapy, for macular oedema following CRVO where the patient has previously been granted an authority prescription for the same eye.

The PBAC considered that the diagnosis of macular oedema secondary to central retinal vein occlusion does not depend solely on the performance of OCT and so the need for the performance of OCT in the requested 'initial' restriction is not adequately justified. The PBAC also did not consider mandatory use of OCT in the 'continuing' restriction adequately supported, given that there may be situations where clinicians do not perform OCT but where continued treatment with aflibercept would be beneficial based on other types of assessment of a patient.

5. Clinical Place for the Proposed Therapy

Retinal vein occlusion is an obstruction of the veins draining blood from the back of the eye, caused by a blood clot (thrombus) or other possible causes such as external compression of the vein or diseases of the vessel wall. Obstruction of one or more of the retinal veins causes blood and fluid to leak from the capillaries that drain into the obstructed vein. This can result in swelling or thickening of the retina (oedema). It is classified into either branch retinal vein occlusion (BRVO) or central retinal vein occlusion CRVO based on the site of venous occlusion. The condition is predominantly unilateral (i.e. affects one eye only). CRVO can be sub-divided into two subtypes: perfused (non-ischaemic) and non-perfused (ischaemic).

The aim of treating macular oedema secondary to CRVO is to maintain and improve visual acuity and prevent long term complications. Early intervention is important because the longer the duration of oedema, the greater the likelihood of permanent structural damage and irreversible vision loss. CRVO is an uncommon condition affecting adults, particularly the elderly.

The PBAC accepted that a clinical need had been identified because there are currently no PBS listed treatments available to treat these patients. The PBAC noted however that there is unsubsidised use of ranibizumab (approved by TGA) and bevacizumab (not approved by TGA for this indication). The submission proposed aflibercept as first-line therapy for macular oedema caused by CRVO.

6. Comparator

The submission nominated placebo/sham injection, as a proxy for best supportive care (BSC), as the main comparator.

The submission also presented an indirect comparison against ranibizumab as supplementary evidence.

Whilst comparisons against BSC and ranibizumab were considered relevant, the PBAC also considered a comparison with bevacizumab to be relevant, because it is currently widely used for the treatment of CRVO and is the therapy most likely to be replaced in practice. Consistent with the PBAC's consideration of ranibizumab in November 2012, the PBAC noted that bevacizumab is not approved by the TGA for central retinal vein occlusion and is not formulated for intravitreal use. The cost-effectiveness of bevacizumab for central retinal vein occlusion is not known because it has not been considered by the PBAC. Thus it would be necessary to establish the cost-effectiveness of bevacizumab as a first step to establish the incremental cost-effectiveness of aflibercept compared to it.

7. Clinical Trials

The submission was based on two direct randomised trials, COPERNICUS and GALILEO, comparing aflibercept to placebo/sham injection. Details of these trials are shown in the table below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
COPERNICUS		
Boyer, D et al.	Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study.	*Ophthalmology* (2012); 119(5):1024-32. Epub March 21, 2012.
Brown, DM et al.	Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study.	*American Journal of Ophthalmology,* (2012); Article in Press.
Gillies, M	Intravitreal VEGF trap-eye in central retinal vein occlusion: Results of the phase 3 Copernicus and Galileo studies.	*Clinical and Experimental Ophthalmology* (2012); 40(S1):44 RANZCO 44th Annual Scientific Congress.
GALILEO		
Holz, F G et al.	VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study.	*British Journal of Ophthalmology (2012)* Epub ahead of print; January 7, 2012.
Gillies, M	Intravitreal VEGF trap-eye in central retinal vein occlusion: Results of the phase 3 Copernicus and Galileo studies.	*Clinical and Experimental Ophthalmology* (2012); 40(S1):44 RANZCO 44th Annual Scientific Congress.

The PBAC noted that while these trials allowed for a comparison of aflibercept and placebo/sham injection, they did not allow for a comparison with ranibizumab, the comparator nominated in the Decision Analytic Protocol (DAP) finalised by the Protocol Advisory Sub-Committee of MSAC. As both arms of both trials included OCT testing to select eligible patients for injection and then monitor them to guide decisions for re-injection, the trials did not provide a comparison that allowed for assessment of the role of OCT testing, or linkage between OCT testing and clinical efficacy of aflibercept. The modelled economic evaluation relied on these two trials.

Both trials had a 21-day screening period, followed by clinic visits every 4 weeks, during which patients were randomised to receive aflibercept or sham injection until the primary endpoint of 24 weeks. The 'as needed' treatment phase, from 24 to 52 weeks, varied between the trials. In the COPERNICUS trial, sham patients were eligible for cross-over to treatment with aflibercept after week 24, whereas cross-over was not possible in GALILEO until week 52. The extension phases also varied between the trials, with the extension period being 52 to 100 weeks in COPERNICUS and 52 to 76 weeks in GALILEO.

8. Results of Trials

The results for the primary endpoint of the COPERNICUS and GALILEO trials, proportion of subjects who gained at least 15 letters in best corrected visual acuity (BCVA) at week 24 across the direct randomised trials, are shown in the table below.

Results of the primary endpoint of proportion of subjects who gained at least 15 letters in best BCVA at week 24

Trial ID	Aflibercept n/N (%)	Sham injection n/N (%)	RD (95% CI)	RR (95% CI)
COPERNICUS	64/114 (56.1%)	9/73 (12.3%)	0.45 (0.33, 0.57)	4.55 (2.42, 8.57)
GALILEO	62/103 (60.2%)	15/68 (22.1%)	0.38 (0.24, 0.52)	2.73 (1.70, 4.38)
Pooled result	126/217 (58.1%)	24/141 (17.0%)	0.41 (0.32, 0.50)	3.37 (2.04, 5.57)
Chi-square for heterogeneity: 1.66, p=0.20 I^2=40%				

BCVA=best corrected visual acuity; RD=risk difference; RR=relative risk

Based on the results of the COPERNICUS and GALILEO trials and the primary outcome of improved BCVA, the PBAC accepted that aflibercept is clinically and statistically significantly more efficacious than placebo.

The PBAC noted that the DAP recommended a secondary evaluation of aflibercept without the use of OCT and that this was not undertaken in the submission. Other than to analyse OCT as a cost resource, the submission did not provide any analysis of the impact of OCT upon the efficacy of aflibercept. The reason for this approach appeared to be that no trials were identified where OCT was not utilised.

Results of the supplementary indirect comparison against ranibizumab are presented in the table below.

Summary of results of the indirect comparison against ranibizumab – proportion of patients gaining ≥15 letters in BCVA

	Aflibercept trials			Ranibizumab trials			
Trial ID	**OR (95% CI)**	**Aflibercept n/N (%)**	**Sham injection n/N (%)**	**Sham injection n/N (%)**	**Ranibizumab n/N (%)**	**OR (95% CI)**	**Indirect OR (95% CI)**
24 weeks – proportion of patients who gained ≥15 letters in BCVA							
COPERNICUS	9.10 (4.13, 20.05)	64/114 (56.1%)	9/73 (12.3%)				
GALILEO	5.34 (2.66, 10.72)	62/103 (60.2%)	15/68 (22.1%)				
Pooled	6.74 (4.00, 11.37)						
CRUISE				22/130 (16.9%)	62/130 (47.7%)	4.35 (2.45, 7.70)	
Indirect	I^2=10%						1.55 (0.71, 3.63)

The PBAC noted the wide confidence intervals from the results of the indirect comparison against ranibizumab, but considered that on balance, aflibercept is likely to be no worse than ranibizumab in regards to comparative efficacy.

With regard to comparative harms, the submission provided only grouped events (i.e. 'treatment emergent' or serious adverse events) and did not provide any information on specific events, in particular ocular-related events. Data for these events were summarised during the evaluation. There were numerically more 'events' reported in aflibercept-treated patients but the differences between aflibercept and sham injection treatment groups were not statistically significant.

The submission provided little detail about post-marketing data or the two trials previously considered by PBAC of aflibercept in age-related macular degeneration. The submission noted that the PBAC would have previously considered these data. Consequently, the submission did not provide any data beyond the trial data that adequately informs an extended assessment of comparative harms. The submission further noted that, as aflibercept was still in the process of gaining TGA registration for the requested indication, further comparative harms data are yet to become available.

9. Clinical Claim

The submission described aflibercept as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over sham injection/placebo (as a proxy for best supportive care). The PBAC considered this claim to be reasonable based on the results of the two trials presented in the submission.

However, the PBAC had concerns over the long-term efficacy of aflibercept for the following reasons:

- The PBAC was unable to assess the longer-term treatment effect of aflibercept for patients who crossed-over (at Week 24 in COPERNICUS and Week 52 in GALILEO) as these data were not available.
- There was deterioration in treatment effect following the initial 24 weeks when dosing was changed to an 'as needed' basis. The clinical trial report for COPERNICUS noted that there appeared to be recurrence of macular oedema when patients switched to 'as needed' dosing.

On the basis of the supplementary indirect comparison of aflibercept versus ranibizumab, the submission described aflibercept as non-inferior in efficacy to ranibizumab and as safe as ranibizumab. The PBAC considered this claim to be reasonable based on comparative week 24 data. However, the PBAC could not draw any conclusions from the week 52 data, because sham-injection patients in both GALILEO and CRUISE were able to cross-over to active treatment following week 24, and the 52 week results provided did not analyse patients according to the duration of treatment. Neither the submission nor the trial reports provided results for patients who commenced active treatment after 24 weeks separately.

The submission's claim of co-dependence between OCT use and aflibercept use was based on 1) the observation that OCT was widely used in clinical trials; 2) the argument that it assists in better targeting aflibercept therapy towards those patients who will benefit most; and 3) that it assists in determining the re-injection requirements during the maintenance treatment phase. The PBAC considered that the diagnosis of CRVO does not depend entirely on OCT performance and that OCT results are not essential to selecting which patient should be eligible for aflibercept. The PBAC also considered that OCT is an aid, used with measurement of visual acuity, in determining whether and when aflibercept should be re-injected. The PBAC was therefore not satisfied that OCT and aflibercept are co-dependent technologies although the PBAC noted that previous advice from ophthalmologists indicated OCT was routinely used for monitoring. The PBAC also noted that the data did not define a clear correlation between change in central retinal thickness and change in visual acuity, with increasing duration between onset of CRVO and treatment initiation noted as also predicting a less favourable change in visual acuity.

10. Economic Analysis

A modelled economic evaluation (cost-utility analysis) was presented based on a superiority claim for comparative benefit of aflibercept over placebo/sham injections. The submission estimated an ICER within the range of $45,000 – $75,000/QALY based on using results for best corrected visual acuity (from the treated eye) from the trial, applied to the trial populations, extrapolated for 36 years (from 12 months trial data) and applying pooled utility weights for both aflibercept and sham injection patients from GALILEO.

The evaluation was structured as a five state Markov model for patients with macular oedema secondary to CRVO from age 64 extrapolated over 36 years and then differentiated to a further three states according to the patient's treatment status, resulting in 15 health states for survivors, plus the usual Markov absorbing health state of death.

The submission chose placebo rather than ranibizumab (as recommended in the DAP) or bevacizumab as the comparator. The PBAC recalled that, when considering the ranibizumab November 2012 submission for macular oedema due to retinal vein occlusion (BRVO or

CRVO), the PBAC considered bevacizumab to be a relevant comparator even though it was not PBS listed or TGA approved. The PBAC considered that an economic comparison against these two active comparators would have been informative.

The PBAC noted that the results of sensitivity analyses indicated that the model was most sensitive to the:

- Duration of the model; (ICER ranging between $45, 000 and greater than $200,000 per QALY gained)
- Age of onset of CRVO;
- Relative risk of mortality with poor vision;
- The use of OCT in the sham treatment arm.

The PBAC considered a base case incremental cost per QALY of between $45,000 and $75,000 as calculated in the submission to be underestimated and unacceptably high in the context of its recent considerations of medicines to treat diseases which impair visual acuity. A consistent question for the Committee has been how evaluations transform trial-based measurements of visual acuity differences into QALY gains.

The PBAC considered that the model was extremely sensitive to the duration of the model of approximately 35 years, and this was unlikely to be applicable to the PBS population. The evidence from Mitchell et al. (1996) used in the submission to describe the PBS population suggested a median age of greater than 80 years, much older than the starting age of 64 years applied in the model. The PBAC considered the argument in the pre-sub-committee and pre-PBAC responses that the Mitchell et al. (1996) data refer to prevalent cases as opposed to newly emergent cases of CRVO as requested in the PBS restriction to be reasonable in explaining the large difference between 80 years and 64 years of age. However, the PBAC still considered that a model duration of approximately 35 years is unlikely to be reflective of real world experience and would require further justification.

The PBAC noted that the evidence used to determine elevated mortality risk associated with unilateral visual impairment, Christ et al. (2008), was based on cross-sectional data, and therefore showed an association rather than a quantifiable causal relationship between visual impairment and death, which may be subject to confounding. The excess mortality risk from this study, estimated as a hazard ratio of 1.23, was considered by the PBAC to be unreliable and likely to be an overestimate, as CRVO usually only affects one eye. The PBAC considered that use of a lower hazard ratio would be more reasonable.

There were also a number of variables that had less individual impact on the estimate of the ICER, but favoured aflibercept. The PBAC noted that the combined effect of a selection of these (age, mortality risk, resolution of macula oedema and utility values) was tested in a multivariate analysis during the evaluation and increased the cost per QALY to the range of $75,000 – $105,000. The PBAC also expressed concern about the estimates of the frequency of aflibercept re-injection on the ICER.

The PBAC therefore considered that the incremental cost per QALY associated with aflibercept treatment would be likely to be higher than the base case incremental cost per QALY calculated by the submission.

11. Estimated PBS Usage and Financial Implications

The submission estimated the overall net cost per year to the PBS/RPBS to be between $10 – $30 million in Year 5.

The PBAC considered that the estimates of use and financial implications presented by the submission were likely to be considerable underestimates. The submission claimed that an uptake rate of 30% for aflibercept is high, but the PBAC noted that there are currently no other PBS-listed treatments for macular oedema secondary to CRVO, and it is likely that the uptake by eligible patients will be greater than 30% in Year 1.

The PBAC also considered that there is a potential for use of aflibercept in patients with macular oedema due to branch retinal vein occlusion, which the PBAC noted is more prevalent than macular oedema secondary to central retinal vein occlusion.

12. Recommendation and Reasons

The PBAC rejected the submission on the basis of an unacceptably high and likely underestimated ICER for aflibercept compared with best supportive care, and, on the basis of inadequate comparative data against either bevacizumab or ranibizumab in the treatment of macular oedema due to CRVO.

The PBAC considered that a resubmission would need to provide comparative efficacy data against bevacizumab and a more formal comparison against ranibizumab, because the PBAC considered that these two drugs are currently being used in practice and would be likely to be replaced by aflibercept if PBS listed.

The PBAC further considered that the duration of the economic model and mortality risk associated with unilateral vision should be more conservative than assumed in the current submission unless further justification could be provided.

The PBAC advised that any resubmission would need to be a major submission.

Outcome:
Reject

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 has no comment.