

7.1 AFLIBERCEPT

**4 mg/0.1 mL injection, 1 x 0.1 mL vial,
4 mg/0.1 mL injection, 1 x 0.09 mL syringe;
Eylea[®]; Bayer Australia Ltd.**

1 Purpose of Application

- 1.1 To extend the current Authority Required listing of aflibercept to include treatment of macular oedema due to central retinal vein occlusion (CRVO). The first submission was July in 2013, followed by a second submission in March 2014.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT				
aflibercept 4mg/0.1mL injection, 1 x 0.1 ml vial	1	5 2	Eylea	BN
aflibercept 4mg/0.1 mL injection, 1 x 0.09 ml pre-filled syringe	1	5 2	Eylea	BN

Category / Program	<i>GENERAL – General Schedule (Code GE)</i>
Prescriber type:	<input type="checkbox"/> <i>Dental</i> <input checked="" type="checkbox"/> <i>Medical Practitioners</i> <input type="checkbox"/> <i>Nurse practitioners</i> <input type="checkbox"/> <i>Optometrists</i> <input type="checkbox"/> <i>Midwives</i>
Episodicity:	
Severity:	
Condition:	<i>Macular oedema secondary to central retinal vein occlusion</i>
PBS Indication:	<i>Macular oedema secondary to central retinal vein occlusion</i>
Treatment phase:	<i>Initial treatment</i>
Restriction Level / Method:	<input type="checkbox"/> <i>Restricted benefit</i> <input checked="" type="checkbox"/> <i>Authority Required - In Writing</i> <input type="checkbox"/> <i>Authority Required - Telephone</i> <input type="checkbox"/> <i>Authority Required – Emergency</i> <input type="checkbox"/> <i>Authority Required - Electronic</i> <input type="checkbox"/> <i>Streamlined</i>
Treatment criteria:	<i>Must be treated by an ophthalmologist</i>

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<p>Clinical criteria:</p>	<p><i>Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)</i></p> <p><i>AND</i></p> <p><i>The condition must be diagnosed by [appropriate diagnostic method – to be finalised]</i></p> <p><i>AND</i></p> <p><i>Patient must have documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (EDTRS) chart</i></p>
<p>Definitions</p> <p><i>(to be finalised at a later stage)</i></p>	<p><i>[Visual impairment is defined as best corrected visual acuity using EDTRS charts] - to be finalised.</i></p>
<p>Prescriber Instructions</p> <p><i>(to be finalised at a later stage)</i></p>	<p><i>Authority approval for initial treatment of each eye must be sought.</i></p> <p><i>The first authority application for each eye must be made in writing or by telephone.</i></p> <p><i>A written application must include:</i></p> <ul style="list-style-type: none"> <i>a) a completed authority prescription form;</i> <i>b) a completed [insert name of form] - PBS Supporting Information Form; and</i> <i>c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.</i> <p><i>A telephone application must be made following submission by facsimile of a copy of a completed [insert name of form] - PBS Supporting Information Form and a copy of the [appropriate diagnostic report]. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised.</i></p> <p><i>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.</i></p>

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<p>Administrative Advice</p> <p><i>(to be finalised at a later stage)</i></p>	<p>Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p><u>Note</u> No increase in the maximum quantity or number of units may be authorised</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised</p> <p><u>Note</u> Special Pricing Arrangements apply.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT				
afibercept 4mg/0.1mL injection, 1 x 0.1 ml vial	1	5 2	Eylea	BN
afibercept 4mg/0.1 mL injection, 1 x 0.09 ml pre-filled syringe	1	5 2	Eylea	BN

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	
Condition:	Macular oedema secondary to central retinal vein occlusion
PBS Indication:	Macular oedema secondary to central retinal vein occlusion
Treatment phase:	Continuing treatment

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Restriction Level / Method:	<input type="checkbox"/> <i>Restricted benefit</i> <input type="checkbox"/> <i>Authority Required - In Writing</i> <input checked="" type="checkbox"/> <i>Authority Required - Telephone</i> <input type="checkbox"/> <i>Authority Required – Emergency</i> <input type="checkbox"/> <i>Authority Required - Electronic</i> <input type="checkbox"/> <i>Streamlined</i>
Treatment criteria:	<i>Must be treated by an ophthalmologist</i>
Clinical criteria: <i>(To be finalised at a later stage)</i>	<i>Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)</i> <i>AND</i> <i>Patient must have previously been granted an authority prescription for the same eye</i>
Prescriber Instructions	<i>(To be finalised at a later stage)</i>
Administrative Advice <i>(To be finalised at a later stage)</i>	<i>Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services</i> <i>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).</i> <u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i> <u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i> <u>Note</u> <i>Special Pricing Arrangements apply.</i>

2.2 As with the March 2014 resubmission, the current resubmission made the claim that aflibercept has superior effectiveness and a similar safety profile compared to placebo for best support care, and that aflibercept has non-inferior safety and effectiveness compared with ranibizumab. The resubmission made no claims about comparative effectiveness or safety compared to bevacizumab, but assumed non-inferior efficacy and superior safety of aflibercept. The resubmission included a cost utility analysis against best supportive care, and cost minimisations against ranibizumab and bevacizumab.

2.3 In comparison with the March 2014 resubmission, the resubmission has removed optical coherence tomography (OCT) from the requested restriction. The resubmission has requested an effective price of ██████ that is ██████ less than the effective price requested in the March 2014 resubmission ██████. The effective price is based on weightings across the three comparisons of BSC ██████, ranibizumab ██████ and bevacizumab ██████.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

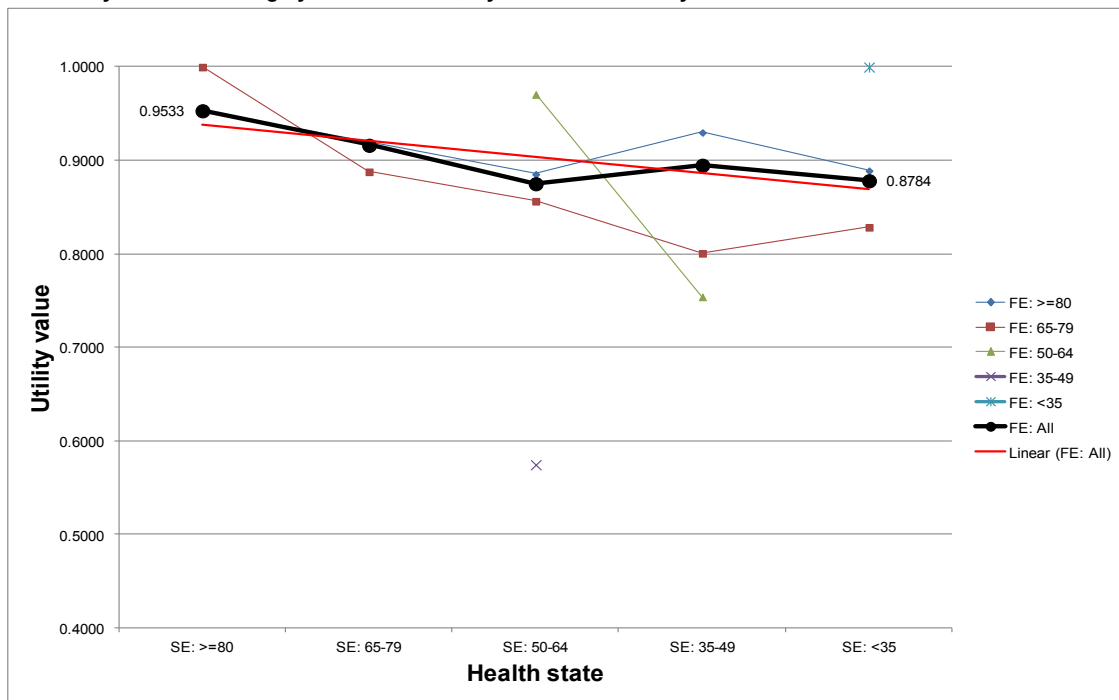
3 Background

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- 3.1 Aflibercept was recommended for registration by the ACPM for visual impairment due to macular oedema secondary to CRVO at the 294th meeting of the ACPM on the 3rd and 4th of October 2014. Aflibercept was TGA registered for the treatment of neovascular (wet) age related macular degeneration in March 2012 and was recommended by the PBAC for treatment of subfoveal choroidal neovascularisation (CNV) due to age related macular degeneration (AMD) in March 2012.
- 3.2 Aflibercept was previously considered for the treatment of CRVO at the July 2013 and March 2014 PBAC meetings. At the July 2013 meeting, the PBAC rejected the submission on the basis of an unacceptably high and likely underestimated ICER compared with best supportive care and on the basis of inadequate comparative data against either bevacizumab or ranibizumab. The PBAC rejected the resubmission at the March 2014 meeting on the basis of an unacceptably high and likely underestimated ICER compared with best supportive care and on the basis of inadequate comparative data against compounded bevacizumab.
- 3.3 The key issues identified in March 2014 PBAC Minutes and the corresponding changes made for the current resubmission are discussed below.
- 3.4 Comparison with bevacizumab: Paragraph 7.2 – The PBAC considered that compounded bevacizumab was also a relevant comparator because evidence of its current use in patients who would be eligible for PBS-subsidised aflibercept means that prescribers would replace compounded bevacizumab in practice with aflibercept if the PBS subsidises aflibercept. The current resubmission provided a comparison with bevacizumab that is used to support the cost-minimisation analysis.
- 3.5 Modelled evaluation – need for model re-specification: Paragraphs 6.33 to 6.41 – the ESC had considered that the link between best corrected visual acuity (BCVA) of the CRVO-affected eye (study eye) and overall utility biases the ICER in favour of aflibercept and that more extensive re-specification of the base case would be needed to account for this structural issue. ESC consequently requested data on the proportions of patients for whom the CRVO-affected eye is the worse or better-seeing eye, and data regarding the patients in each arm for whom the CRVO affected eye improves from being the worse-seeing eye to the better-seeing eye (p11 March 2014 ESC Advice). The PBAC agreed with ESC regarding the bias in the model and noted ESC's request for additional data (paragraphs 6.35 and 6.36, March 2014 PBAC Minutes). The current resubmission provides data from the GALILEO trial on fellow eye transitions, fellow eye better-seeing status, utilities and health states defined by fellow eye BCVA.
- 3.6 The figure below shows that the trial data are most informative about how the visual acuity (VA) of the study eye affects utility when the fellow eye has BCVA >80 and 65-79. The ESC noted that these data show that the relationship between utility and VA in study eye is weak, but in the expected direction for people with VA in fellow eye > 80 (though it is noted that it is not monotonic) and stronger in people with VA in fellow eye of 65-79. This confirmed the view of ESC and PBAC in the context of the previous submission – that quality of life depends on overall visual acuity, which is most likely to be determined by the best seeing eye.

- 3.7 However the ESC further noted that the data also demonstrated that there is limited information to inform the impact of improving VA in the study eye in people with poor VA in the fellow eye. The ESC agreed with the commentary that It must be made clear that utility estimates do not appear robust, and both the utilities used in the model and those used in justifying the present model structure are highly sensitive to the way they have been arithmetically derived and may not reflect the actual quality of life improvements from aflibercept treatment as the resubmission claims in its argument against model re-specification.
- 3.8 The ESC also noted that there are relatively few patients populating some of these different health states and contributing to the difference. The linear extrapolation appears to be a simple average across all observations (in fact a linear extrapolation of the black line, which is the utility associated with the study eye’s visual acuity not controlling for the fellow eye), and therefore averaged across all fellow eye states – it would be more appropriate to undertake a weighted average.

Utility value of seeing eye health states, by BCVA of fellow eye



Source: Submission Section C Figure 11 p 03

For more detail on PBAC’s view, see section 7 “PBAC outcome”

4 Clinical place for the proposed therapy

- 4.1 Central retinal vein occlusion is a blockage of the vessel which drains blood out of the retina, the light-sensitive tissue at the back of the eye. The blockage results in increased pressure within the blood vessel causing blood and fluid to leak from the blood vessels into the retinal potentially leading to macular oedema.
- 4.2 Aflibercept will likely replace ranibizumab and off-label intravitreal bevacizumab.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 As in the March 2014 resubmission, the current resubmission nominated best supportive care as the comparator, and ranibizumab as a secondary comparator. Given that ranibizumab has received a positive recommendation from the PBAC (July 2014) for the treatment of CRVO, the ESC considered that the most relevant comparison is between aflibercept and ranibizumab.
- 5.2 The sponsor did not accept bevacizumab as a clinical comparator for aflibercept in CRVO, but an economic comparison was presented in the submission. No formal clinical claim was made to support the cost minimisation analysis.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with aflibercept, including the following:
- reducing out-of-pocket costs which can be barrier to people commencing or maintaining ongoing treatment;
 - expands the range of treatment options for patients and clinicians; and
 - timely treatment with VEGF inhibitors will be important in maximising patient's participation in the economy, and minimising their demand for other services.

Clinical trials

- 6.3 The resubmission was based on the same two trials (GALILEO and COPERNICUS) presented in the July 2013 and March 2014 resubmissions, comparing aflibercept to sham injection.
- 6.4 Details of the trials presented in the resubmission are provided in the table below.

Trials and associated reports presented in the resubmission

Trial ID/ first author	Protocol title/ publication title	Publication citation
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Trial ID/ first author	Protocol title/ publication title	Publication citation
COPERNICUS	<p>•A Randomized, Double Masked, Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (COPERNICUS) 24 Week data. 06 June 2011, Regeneron Pharmaceuticals, Inc.</p> <p>•A Randomized, Double Masked, Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (COPERNICUS) 52 Week data. 21st August 2012, Regeneron Pharmaceuticals, Inc.</p> <p>•A Randomized, Double Masked, Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (COPERNICUS) 100 Week data. 19 October 2012, Regeneron Pharmaceuticals, Inc.</p> <p>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.</p> <p>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.</p> <p>Gillies, M. Intravitreal VEGF trap-eye in central retinal vein occlusion: Results of the phase 3 Copernicus and Galileo studies.</p>	<p>Ophthalmology 2012; 119(5):1024-32. Epub March 21, 2012.</p> <p>American Journal of Ophthalmology 2012; article in press.</p> <p>Clinical and Experimental Ophthalmology 2012; 40(S1):44</p> <p>RANZCO 44th Annual Scientific Congress.</p>
GALILEO	<p>•A Randomized, Double-masked, Sham-controlled Phase-3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (GALILEO) 24 Week data. 15 August 2011, Bayer HealthCare.</p> <p>A Randomized, Double-masked, Sham-controlled Phase-3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (GALILEO) 52 Week data. 15 August 2012, Bayer HealthCare.</p>	<p>British Journal of Ophthalmology (2012) Epub ahead of print; January 7, 2012.</p> <p>Clinical and Experimental Ophthalmology 2012; 40(S1):44</p> <p>RANZCO 44th Annual Scientific Congress.</p>

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Trial ID/ first author	Protocol title/ publication title	Publication citation
	<p>•A Randomized, Double-masked, Sham-controlled Phase-3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) (GALILEO) 76 Week data. 08 October 2012, Bayer HealthCare.</p> <p>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.</p> <p>Gillies, M. Intravitreal VEGF trap-eye in central retinal vein occlusion: Results of the phase 3 Copernicus and Galileo studies.</p>	
CRUISE	<p>Brown, DM, Campochiaro, PA, Singh, RP, et al. Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Six-Month Primary End Point Results of a Phase III Study.</p> <p>Campochiaro PA, Brown DM, Awh CC et al. Sustained Benefits from Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study.</p>	<p>Ophthalmology 2010; 117(6):1124-33</p> <p>Ophthalmology 2011; 118(10):2041-9</p>

Source: Table 11, p178 of the March 2014 resubmission

6.5 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in economic model
Aflibercept versus sham injection						
COPERN- ICUS	187	R, DB 100 wks	Low	Patients with $\geq 250\mu\text{m}$ CST as measured by OCT and an ETDRS BCVA of 20/40 to 20/320	Proportion of patients with ≥ 15 letter gain in BCVA at 24/52	Used
GALILEO	171	R, DB 76 wks	Low			Used
Ranibizumab versus sham injection used for the indirect comparison						
CRUISE	392	R, DB	Low	Patients with $\geq 250\mu\text{m}$ CST as measured by OCT and a Snellen equivalent BCVA of 20/40 to 20/320	Mean change from baseline in BCVA at Month 6	Not used

Abbreviations: BCVA=best corrected visual acuity; CST=central subfield thickness; DB=double blind; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; R=randomised.

Source: compiled during the evaluation

Comparative effectiveness

6.4 The PBAC has previously accepted the claim that aflibercept has superior effectiveness and a similar safety profile to placebo. However, the PBAC remained concerned about the long-term efficacy of aflibercept, considering the previous resubmission did not provide any evidence relating the revised loading dose (three

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doses given monthly) to longer term clinical efficacy (paragraph 7.5, March 2014 PBAC minutes).

Results of the primary endpoint of proportion of subjects who gained at least 15 letters in best BCVA at week 24 – aflibercept vs sham injection

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%				

Source: Table 27, p106 of the July 2013 submission

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

- 6.5 The PBAC has also previously accepted the claim that aflibercept is non inferior in terms of efficacy and safety compared to ranibizumab (paragraph 6.29, March 2014 PBAC minutes). The table below presents the results of the indirect comparison of efficacy of aflibercept versus ranibizumab.

Results of the indirect comparison - proportion of patients who gained ≥15 letters in BCVA – aflibercept vs ranibizumab

Trial ID	Aflibercept trials			Ranibizumab trials			Indirect OR (95% CI)
	OR (95% CI)	Aflib n/N (%)	Sham n/N (%)	Sham n/N (%)	Ranib n/N (%)	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)	1.55 (0.71, 3.63)
Indirect	I ² =10%						
52 weeks – proportion of patients who gained ≥15 letters in BCVA							
COPERNICUS	3.16 (1.66, 6.02)	63/114 (55.3%)	22/73 (30.1%)				
CRUISE				43/130 (33.1%)	66/130 (50.8%)	2.09 (1.26, 3.45)	
Indirect	I ² =0%						1.51 (0.67, 3.43)

Source: Table 12 and Table 13, p50 of Appendix D.2 of the July 2013 submission; Table 35 and 36, p165 of the resubmission
BCVA=best corrected visual acuity; OR=odds ratio

- 6.6 The PBAC has previously accepted, on the basis of an analysis conducted during the March 2014 evaluation, that aflibercept is non-inferior in terms of efficacy compared to bevacizumab. The table below presents the results of the indirect comparison conducted during the March 2014 evaluation.

Indirect meta-analysis of the proportion of subjects who gained at least 15 letters in BCVA at Week 24 – aflibercept vs bevacizumab

Outcome	Aflibercept vs. sham OR (95% CI)	Bevacizumab vs. sham OR (95% CI)	Aflibercept vs. bevacizumab OR (95% CI)	P-value
Proportion of patients gaining ≥ 15 letters in BCVA at Week 24	6.74 (4.00, 11.37)	6.00 (1.89, 19.04)	1.123 (0.32, 3.99)	0.8573

Source: Calculated during the March 2014 evaluation.

Comparative harms

6.7 The PBAC noted that the trial data showed minimal differences in adverse events between aflibercept and sham injection in the COPERNICUS and GALILEO trials (paragraph 6.19, March 2014 resubmission).

Benefits/harms

6.8 A summary of the comparative benefits and harms for aflibercept versus sham injection (as a proxy for BSC) is presented in the table below.

Summary of comparative benefits and harms for aflibercept and sham injection

Trial	Aflibercept	Sham injection	RR* (95% CI)	Event rate/100 patients		RD* (95% CI)
				Aflibercept	Sham injection	
Benefits						
Gain ≥ 15 letters in BCVA						
GAL & COP ^a	126/217	24/141	3.37 (2.04, 5.57)	58.1	17.0	0.41 (0.32, 0.50)
Harms						
Intraocular pressure increased						
GAL & COP ^a	17/218	9/142	1.22 (0.55, 2.67)	7.8	6.3	0.01 (-0.04, 0.07)
Conjunctival haemorrhage						
GAL & COP ^a	26/218	6/142	1.08 (0.51, 2.27)	11.9	4.2	0.02 (-0.05, 0.09)
Hypertension						
GAL & COP ^a	14/218	7/142	1.29 (0.53, 3.14)	6.4	4.9	0.01 (-0.04, 0.06)

* RR and RD calculated using Stats Direct Version 2.7.9; ^a pooled results of COPERNICUS and GALILEO trials; Source: harms compiled from Table 19 p104 of the resubmission

6.9 On the basis of the GALILEO and COPERNICUS trials, for every 100 patients treated with aflibercept in comparison to sham injection:

- approximately 41 additional patients would experience a gain of at least 15 letters in visual acuity over 24 weeks
- approximately one or two additional patients would experience an increase in intraocular pressure
- approximately eight additional patients would experience conjunctival haemorrhage
- approximately one or two additional patients would experience hypertension.

6.10 A summary of the comparative benefits and harms for aflibercept versus ranibizumab is presented in the table below.

Summary of comparative benefits and harms for aflibercept and ranibizumab

Benefits						
24 weeks – proportion of patients who gained ≥ 15 letters in BCVA						
	AFB or RBZ vs sham		Indirect comparison: AFB vs RBZ			
	N	OR (95% CI)	OR (95% CI)			
GALILEO and COPERNICUS pooled results	358	6.74 (4.00, 11.37)	1.55 (0.71, 3.63)			
CRUISE	260	4.35 (2.45, 7.70)				
Harms						
Trial	AFB	RBZ	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				AFB	RBZ	
Myocardial infarction						
GALILEO and COPERNICUS pooled results	0/114	-	-	0.0	-	-0.05 (-0.13, -0.02)
CRUISE	-	1/129	-	-	0.8	0.0 (-0.02, 0.02)
Indirect comparison: aflibercept vs ranibizumab			0.22 (0.00, 14.58)	-		-0.01 (-0.05, 0.03)
Cataract						
GALILEO and COPERNICUS pooled results	1/114	-	-	0.9	-	0.01 (-0.02, 0.04)
CRUISE	-	2/129	-	-	1.6	-0.02 (-0.04, 0.01)
Indirect comparison: aflibercept vs ranibizumab			9.8 (0.12, 789.22)	-		0.03 (-0.01, 0.07)

AFB=aflibercept; BCVA=best corrected visual acuity; OR=odds ratio; RBZ=ranibizumab; RD=risk difference; RR=risk ratio; Source: Compiled during the evaluation

- 6.11 On the basis of the indirect evidence using sham injection as the common comparator, there appears to be no difference in benefits and harms between aflibercept in comparison to ranibizumab.

Clinical claim

- 6.12 As in the March 2014 resubmission, the current resubmission claimed that aflibercept has superior effectiveness with a similar safety profile compared to placebo, and that aflibercept is non-inferior in terms of efficacy and safety compared to ranibizumab. No clinical claims were made regarding safety or efficacy of aflibercept in comparison to bevacizumab, but the resubmission noted that the PBAC has considered aflibercept and bevacizumab to be non-inferior in terms of efficacy (paragraph 6.29, March 2014 PBAC minutes). The resubmission also included a cost-minimisation analysis that assumes fewer adverse events in aflibercept.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.13 Three economic evaluations were presented by the resubmission:

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- (1) cost utility analysis (CUA) comparing aflibercept and BSC (aflibercept vial price = [REDACTED])
- (2) cost minimisation analysis (CMA) comparing aflibercept and ranibizumab (aflibercept vial price = [REDACTED])
- (3) cost minimisation analysis comparing aflibercept and bevacizumab (aflibercept vial price = [REDACTED])

6.14 CUA aflibercept vs. BSC: In comparison to the March 2014 model, the current model reduced the model duration from 28 to 15 years, the modelled recurrence of macular oedema and the number of loading doses from 3 to 6. The tables below summarise the changes made to economic model and the model structure across the three submissions.

Summary of changes made to economic model across three submissions

Changed parameter	Submission		
	July 2013	March 2014	November 2014
Effective price	[REDACTED]	[REDACTED]	[REDACTED]
Cost of OCT	\$250	\$91.75. Separate base cases including and excluding OCT costs from the BSC model arm.	\$91.75
Number of loading doses	6	6	3
Mortality risk of unilateral blindness	HR = 1.23	HR = 1.13	HR = 1.13
Risk of disease recurrence	0	0	0.025 every 4 years
Age of onset (model duration)	64 years (36 years)	72 years (28 years)	72 years (15 years)

BSC= best supportive care; HR= hazard ratio; OCT= optical coherence tomography

Source: Compiled during the evaluation

Summary of model structure and rationale

Component	Summary
Time horizon	15 years in the model base case versus 52 weeks in the trial
Outcomes	Patient with +15 letters gain from baseline; QALYs
Methods used to generate results	Directly trial-based to week 52, then Markov modelled outcomes to life expectancy.
Health states	5 health states defined by the visual acuity of the CRVO affected eye of patients treated with aflibercept, patients on BSC, and patients whose macular oedema has resolved, plus the absorbing health state death for a total of 16 health states.
Utilities	Trial-based (GALILEO) EQ-5D values pooled at baseline, 24 and 52 weeks, with linear interpolation used to account for differences in health state 4.
Cycle length	4 weeks
Transition probabilities	Trial data to weeks 0-52, then transition matrices derived from Hayreh et al., (2011) for macular oedema resolution >52 weeks, Klein et al (1991) for loss of VA due to age, and Christ et al (2008) for RR of mortality.

Source: compiled during the evaluation

6.15 The ESC noted that the model maintained the assumption that the treatment effect in recurrent CRVO is the same as the original episode, and that ‘sham treated patients achieve the same level of effectiveness in the recurrent episode.’ The resubmission claimed that this assumption is necessary due to lack of evidence on the effect of aflibercept on recurrent CRVO and a technical issue (lack of memory) in the Markov model). The ESC noted that this assumption likely favours aflibercept, and the extent of this bias is not known. But if the underlying approach and probability estimate are accepted, this assumption will have a minimal impact on the ICER.

- 6.16 The ESC also noted that in terms of model duration, the model now incorporates recurrence of macular oedema due to RVO in the same eye, and that approximately [redacted] of patients will experience recurrence within the 15 year model duration. Modelling for RVO recurrence addresses part of the issue. After treatment is ceased, the revised model assumes that some patients ([redacted] over model duration) will have recurrence of RVO, and will be re-allocated to their original treatment (afibercept or sham) and follow the original transition probabilities. Considering the small probability of recurrence, this has minimal impact on the ICER. For those who do not have RVO recurrence, they are assumed to have natural VA decline reflecting the general population. The resubmission presented no evidence to support this assumption, and considering that patients with CRVO consist of a group of patients with pre-existing ocular problems, it appears they are likely to suffer related, (not necessarily RVO) ocular problems that would cause VA to decline significantly more rapidly than naturally. A model that accounted for this would either change the extrapolated VA decline curve, or use a much larger probability in the recurrence variable. Given that there is no clinical evidence to support the assumption that aflibercept treatment is equally effective in recurrent cases as in new cases of CRVO, it would also be informative to assess different efficacy rates, as assuming treatment is equally effective biases the model in favour of aflibercept.
- 6.17 The resubmission did not re-specify the economic model to account for the VA of the fellow eye. The resubmission presented additional data on the baseline BCVA of the fellow eye, transitions in fellow eye BCVA, and fellow eye better seeing and worse seeing status, as well as data on EQ-5D estimates by fellow eye BCVA. The argument was made that the majority of fellow eyes are healthy, better-seeing and remain so throughout the GALILEO trial, and hence would have no effect on the model. The ESC agreed with the commentary that the data presented by the submission did not address the issue due to limited variability and change in the fellow eye i.e. a case needs to be made regarding generalisability of these data. The ESC was of the view that the interpretation of these data are that the utility changes observed in the GALILEO trial are informative in terms of the impact of an improvement in the seeing eye conditional upon good and stable VA in the fellow eye. The analyses arguing against model re-specification were noted to be based on solely GALILEO transition probabilities and baseline BCVA, while the model was based on both GALILEO and COPERNICUS baseline and transition probabilities.
- 6.18 The table below presents a summary of the key drivers of the model.

Key drivers of the model

Description	Method/Value	Impact
Time horizon	15 years; assumed from 6 month trial duration	High, favours aflibercept
Dose intensity	3 loading doses, then GALILEO post 6 month injection frequency assumed	High, favours aflibercept
Excess mortality risk of unilateral blindness	RR=1.13 from Christ et al 2008	High, favours aflibercept

Source: compiled during the evaluation

- 6.19 The table below presents the results of the resubmission's economic evaluation.

Results of the economic evaluation

Component	Aflibercept	BSC	Increment
Costs	█	█	█
QALYs	█	█	█
Incremental cost/QALY gained (November 2014)			█

BSC=best supportive care; QALY= quality adjusted life-year

Source: Table 34, pp 134 of the November 2014 resubmission

6.20 The base case ICER of the current resubmission (█ \$15,000 - \$45,000/QALY gained) is lower than the ICER of the March 2014 resubmission (█ with OCT costs in BSC arm; █ with no OCT costs for BSC).

6.21 CMA aflibercept vs. ranibizumab: the equi-effective doses were estimated as █ aflibercept injections over the first year of treatment and █ ranibizumab injections over the first year of treatment. These estimates were based on ranibizumab injection frequency from the CRUISE trial and injection frequencies from the GALILEO and COPERNICUS trials (using 6 loading doses). The ESC noted this approach was inconsistent with the loading doses used in the economic model and the bevacizumab cost-minimisation, which both assumed 3 loading doses.

Comparison of treatment costs of aflibercept and ranibizumab: under the three dosing dose regimen for aflibercept

Treatment period (months)	Aflibercept (3 loading doses)	Aflibercept (6 loading doses)	Ranibizumab (6 loading doses)
1 – 3	█	█	█
4 – 6	█ (assumption based on the dose frequency observed in the 7-12 month period)	█	█ (as per the PI)
7 – 12	█ (based on GALILEO and COPERNICUS)	█	█ (based on CRUISE)
Total injections in the first 12 months of treatment	█	█	█
Price premium relative to ranibizumab	█	█	█

Source: Table 37, p142 of the November 2014 resubmission

6.22 The resubmission estimated an █ price premium over ranibizumab based on its estimates of equi-effective dosing. The cost-minimising price (DPMQ) presented by the resubmission for aflibercept versus ranibizumab was █ (█). The █ price premium was suggested to likely reflect the upper bound of the possible injection ratio between ranibizumab and aflibercept, due to vague continuing criteria in the restriction of aflibercept and the lack of clinical evidence around aflibercept reinjection frequencies under a 3 loading dose regimen, and price parity (rather than the █ price premium) was suggested to likely reflect the lower bound of equi-effective dosing estimates.

6.23 The PSCR (p3) claimed that this dose relativity premium did not rely upon the difference in the number of aflibercept and ranibizumab loading doses, but was instead based on the 12-month injection frequency as observed in the GALILEO, COPERNICUS and CRUISE trials where both aflibercept and ranibizumab used 6 loading doses in all three trials. The ESC agreed with the commentary that the dose

relativity underpinning the premium is not adequately supported, and therefore is not likely to be reasonable.

- 6.24 In terms of the TGA-revised Product Information in relation to the loading dose, the trial evidence presented by the resubmission to support the revised loading dose regimen (from 6 to 3 loading doses) was the mean change from baseline in COPERNICUS and GALILEO trials which was provided as an attachment in the March 2014 resubmission. The current resubmission stated that, in both the GALILEO and COPERNICUS trials, the progression of improvement in VA showed a steep initial rise, with most of the improvement becoming evident after the first three injections. The submission further stated that the findings from the trials suggest that, in some patients, most of the visual acuity gains could be achieved with the first three injections and, for these patients, considerations may be given to switch the dosing regimen to the maintenance phase to individualise the treatment interval. The ESC considered that the major concern is not with the loading doses, but rather the injection frequency estimates after the loading phase. The resubmission's reliance on injection rates after 6 months was based on the assumption that maintaining the effect reached after 3 months will require the same frequency injections as after 6 months. The ESC agreed that this assumption was not supported.
- 6.25 The ESC questioned how the treat and extend regimen would function in clinical practice. While beginning treat and extend after only 3 loading doses does allow flexibility, and could reduce the number of injections in the first six months as compared to the 6 loading dose regimen, no satisfactory evidence has been provided to support using post six month re-injection rates as a proxy for re-injections in the three months after the revised 3 month loading doses. The ESC agreed with the commentary that this is a concern in the economic evaluation of aflibercept compared to sham and the cost-minimisation against bevacizumab.
- 6.26 The issue was further compounded by the fact that the current resubmission removed the OCT requirements from treatment continuation and suggested little continuing treatment criteria in general. While the reasons for removing OCT may be justified, its absence removes a criterion for treatment continuation. This would give physicians less objective requirements in determining the treatment schedule and thus makes estimating the number of re-injections in clinical practice more difficult.
- 6.27 CMA aflibercept vs. bevacizumab: the equi-effective doses were estimated as [REDACTED] aflibercept injections over the first year of treatment and [REDACTED] bevacizumab injections over the first year of treatment based on the Epstein 2012 sham-controlled randomised trial regimen of one 1.25 mg dose every 6 weeks. No formal clinical claim is made to support the CMA. The ESC questioned the inclusion of adverse event costs in the CMA given the non-systematic approach used by the resubmission and the lack of evidence informing the long-term systemic adverse events across the VEGF inhibitors.

Cost minimisation price of aflibercept compared to bevacizumab

Parameter	Bevacizumab	Aflibercept
Drug cost per injection	[REDACTED]	[REDACTED]
Administration cost/injection	[REDACTED]	[REDACTED]
Drug and administration cost/injection	[REDACTED]	[REDACTED]
Injections per patient: Year 1	[REDACTED]	[REDACTED]

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Total drug and administration costs per patient: Year 1					
Adverse event costs					
Total costs per patient: Year 1					

Source: Table 41, p158 of the November 2014 resubmission

- 6.28 The ESC noted a recent Cochrane review by Moja et al 2014 concluded that the systemic safety of bevacizumab for neovascular AMD is similar to that of ranibizumab, except for gastrointestinal disorders, which was a part of a secondary analysis.
- 6.29 The submission requested a price premium for aflibercept (██████████ per vial) on the basis of costs associated with research and development, registration, reimbursement, patient support and pharmacovigilance. This resulted in a proposed aflibercept vial price of ██████████ for the comparison with bevacizumab. The PBAC considered that a price premium for aflibercept based on costs associated with registration, reimbursement, patient support and pharmacovigilance was not relevant for the CMA.
- 6.30 On the basis of the aflibercept vial prices used in the economic evaluations, the overall effective price ██████████ was informed by a ██████████ distribution across ranibizumab/bevacizumab/BSC as comparators.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Drug cost/patient/year: ██████████ in year 1; ██████████ each subsequent year through to year 5.

- 6.31 The estimated drug cost/patient/year was based on an average number of aflibercept injections per patient each year (year 1: ██████████; years 2-5: ██████████). The resubmission contended that almost all patients do not require treatment beyond 5 years. Estimates of injection frequency after the loading dose phase were not well supported.

Estimated PBS usage & financial implications

- 6.32 This resubmission was not considered by DUSC.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	██████████	██████████	██████████	██████████	██████████
Number treated – March 2014	██████████	██████████	██████████	██████████	██████████
Uptake rate	██████████	██████████	██████████	██████████	██████████
Uptake rate March 2014	██████████	██████████	██████████	██████████	██████████
Injections	██████████	██████████	██████████	██████████	██████████
Injections - March 2014	██████████	██████████	██████████	██████████	██████████
Estimated net cost to PBS/MBS					
Net cost to PBS	██████████	██████████	██████████	██████████	██████████
Net cost to March	██████████	██████████	██████████	██████████	██████████

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	Year 1	Year 2	Year 3	Year 4	Year 5
2014					
Net cost to MBS					
Net cost to MBS March 2014					
Estimated total net cost					
Net cost PBS/MBS					
Net cost PBS/MBS March 2014					

Each patient is estimated to use [redacted] injections in year 1 and [redacted] injections per year in years 2 through 5
Source: Compiled during the evaluation

The redacted table above shows:

Estimated patient numbers: less than 10,000 in Year 1, increasing to less than 10,000 per year in Year 5;

Estimated injections: less than 10,000 in Year 1, increasing to 10,000 – 50,000 in Year 5;

Estimated financial impact: Cost of less than \$10 million per year in Year 1, increasing to a cost of \$10 - \$20 million per year in Year 5.

- 6.33 Compared to the March 2014 resubmission, the current resubmission revised uptake rates upwards, and revised injection frequency downwards. Total cost estimates were similar to the March 2014 resubmission due to a reduction in requested price, and the aforementioned reduction in injections. These estimates depended on the assumption that ranibizumab is not PBS-listed, and on the assumption of 3 loading doses followed by dosing according to post 6-month GALILEO injection rates, which were not clinically supported and may be underestimates.
- 6.34 The PSCR (p4) included financial estimates for a 'worst case' scenario where all aflibercept patients use 6 loading doses. The PSCR noted that this would increase net PBS/RPBS expenditure by [redacted] in the fifth year of listing relative to the 3 loading dose estimates in the resubmission.

Combined PBS/RPBS expenditure assuming three and six loading dose regimens

	Year 1	Year 2	Year 3	Year 4	Year 5
Three loading dose regimen ^a					
Six loading dose regimen ^b					
Difference in PBS expenditure ^c					

^a See 7.1.COM.76, Table E.4.1.

^b Calculated for the PSCR (Change cell D51 in the 'Background and Assumptions' worksheet from [redacted]).

^c Difference in PBS expenditure is greater in the early years because there are more new patients in the loading dose phase of treatment.

Source: Table 6, p6 of the PSCR

Financial Management – Risk Sharing Arrangements

- 6.35 The resubmission did not provide detail of a risk sharing arrangement, [redacted] demonstrated to be cost-effective against the relevant comparator(s) for each indication.
- 6.36 The PBAC noted that as the re-submission did not propose a risk sharing arrangement, to address the concerns regarding re-injections beyond the loading

dose phase, the PBAC recommended that a subsidisation cap for aflibercept for this indication would be necessary. [REDACTED]

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of aflibercept as Section 85 Authority required benefit to include treatment of a patient with macular oedema due to central retinal vein occlusion (CRVO). The PBAC considered that authority applications through the PBS and Specialised Drugs Branch of the Department of Human Services would be appropriate for aflibercept, similar to administrative arrangements for ranibizumab and aflibercept in AMD.
- 7.2 The PBAC recommended the listing of aflibercept on a cost-minimisation basis with ranibizumab. The PBAC determined that the equi-effective doses are aflibercept 2 mg injection : 0.5 mg ranibizumab injection.
- 7.3 The PBAC concluded that, based on the totality of the available clinical evidence, aflibercept can also be considered non-inferior in terms of effectiveness and safety with bevacizumab. The equi-effective doses for this comparison and aflibercept 2 mg injection : 1.25 mg bevacizumab injection. The PBAC noted the bevacizumab equi-effective dose for this submission is different with the submission for aflibercept for diabetic macular oedema (DME) also considered on the November 2014 agenda (item 6.2 refers). The PBAC considered that this was due to the different trial data available for bevacizumab for each indication.
- 7.4 The PBAC considered that the data provided did not enable any further differentiation across these three alternative VEGF inhibitors by dose frequency or treatment duration for CRVO.
- 7.5 The PBAC noted that the resubmission removed OCT from the requested restriction. The PBAC advised that the restriction wording for aflibercept needs to include the following information:
- criteria (trial based) for patients to be eligible for treatment must be consistent with ranibizumab;
 - a documentation of assessment of response (at each visit) to establish eligibility for continuation or cessation of treatment;
 - appropriate method(s) to assess response; and
 - if possible, duration of treatment.
- The PBAC requested the Department to work with the Restriction Working Group to finalise a restriction wording.
- 7.6 The PBAC noted the clinical place for aflibercept as being an alternative to ranibizumab and bevacizumab (off label) for the treatment of CRVO.

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- 7.7 The PBAC recalled that in March 2014 it had previously considered best supportive care as the appropriate comparator for aflibercept. Given that ranibizumab received a positive recommendation in July 2014 for the treatment of CRVO, the PBAC agreed that ranibizumab is now the most relevant comparator. As in the March 2014 re-submission, the PBAC remained of the view that bevacizumab is also a relevant comparator.
- 7.8 The PBAC's views on aflibercept's non-inferiority in terms of comparative effectiveness and safety against ranibizumab remained unchanged from those formed in July 2013 and March 2014 meetings. The PBAC noted that no clinical claims were made by the re-submission regarding the safety or effectiveness of aflibercept in comparison to bevacizumab however, the PBAC recalled the March 2014 consideration where it accepted that, on the basis of the analysis conducted during the evaluation, aflibercept is non-inferior in terms of effectiveness compared to bevacizumab (paragraph 6.29, March 2014 PBAC Minutes).
- 7.9 The PBAC noted that the submission provided no formal clinical comparison was made to support its cost-minimisation analysis against bevacizumab. The submission identified one randomised trial in CRVO comparing bevacizumab 1.25 mg and sham (Epstein 2012), which could establish equi-effective doses by indirectly comparing injection numbers for aflibercept and bevacizumab via sham. On the totality of the evidence available, it is reasonable to conclude non-inferiority across all three VEGF inhibitors.
- 7.10 The PBAC noted that the submission presented three economic evaluations: a cost-utility analysis based on the comparisons of aflibercept versus best supportive care, two cost-minimisation analyses comparing aflibercept versus ranibizumab and aflibercept versus bevacizumab. Given the acceptance of equivalence in effectiveness and safety between aflibercept and ranibizumab (paragraph 7.6), the PBAC considered that the primary analysis should be a cost-minimisation to ranibizumab and cost-minimisation to bevacizumab as a secondary analysis.
- 7.11 The PBAC did not accept the submission's proposed pricing approach where the price of aflibercept is the overall aflibercept vial price calculated by a weighting across the ranibizumab, BSC and bevacizumab comparisons.
- 7.12 The PBAC considered the issues in the cost-minimisation analysis between aflibercept and ranibizumab, as reported in paragraphs 6.22 to 6.23. The PBAC did not accept the re-submission's request of an [REDACTED] premium against ranibizumab on the basis that the dose relativity underpinning the price premium is not adequately supported. The PBAC noted that in its Pre-PBAC Response, the sponsor is willing to concede the [REDACTED] price premium and accepted a 1:1 dose relativity (price parity) to ranibizumab should ranibizumab become listed on the PBS.
- 7.13 The PBAC noted that ranibizumab was recommended for both CRVO and BRVO. The PBAC recommended that the Department should ensure that the cost-minimisation comparison of aflibercept to ranibizumab should only be for the CRVO indication. The Pre-PBAC Response also commented on this issue and assumed the relative prevalence of CRVO to BRVO is 1:2.8 (Mitchell et al., 1996:BMES), and estimated that the ranibizumab RVO price (weighted across both CRVO and BRVO) would be around [REDACTED] less than the price for the CRVO component.

- 7.14 The PBAC noted the issues around the safety advantages of aflibercept over bevacizumab. The PBAC noted the inclusion of bevacizumab adverse events costs in the model which was based on two trials (IVAN and CATT) comparing bevacizumab and ranibizumab in the treatment of AMD, i.e. the submission concludes that any differences in systemic adverse events evident in bevacizumab compared to ranibizumab, can reasonably be assumed to be associated with bevacizumab and not aflibercept. The PBAC did not accept this assumption given the lack of direct evidence and presumptive basis for the consideration of IVAN and CATT trials. Furthermore, the PBAC noted a recent Cochrane review by Moja et al 2014 which found the systemic safety of bevacizumab for neovascular AMD to be similar to that of ranibizumab, except for gastrointestinal disorders, which was a part of a secondary analysis.
- 7.15 The PBAC considered the issues in the cost-minimisation analysis between aflibercept and bevacizumab. The PBAC did not accept the re-submission's request for a price premium based on costs associated in registration, reimbursement, patient support and pharmacovigilance, noting that these were not relevant to the cost-minimisation analysis.
- 7.16 The PBAC noted the issues in the revised financial estimates. The PBAC considered that the estimated number of injections per patient per year have important consequences for estimated costs. The PBAC acknowledged that the TGA Product Information has been updated to reduce the number of monthly injections from six to three in the loading dose phase, however re-injections after three months remain a source of uncertainty considering the lack of new sources of evidence.
- 7.17 The PBAC advised that aflibercept is not suitable for prescribing by nurse practitioners.
- 7.18 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Suggested wording for the restriction (final restriction to be finalised).

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT				
aflibercept 4mg/0.1mL injection, 1 x 0.1 ml vial	1	5 2	Eylea	BN
aflibercept 4mg/0.1 mL injection, 1 x 0.09 ml pre-filled syringe	1	5 2	Eylea	BN

Category / Program	<i>GENERAL – General Schedule (Code GE)</i>
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	
Condition:	<i>Macular oedema secondary to central retinal vein occlusion</i>
PBS Indication:	<i>Macular oedema secondary to central retinal vein occlusion</i>
Treatment phase:	<i>Initial treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<i>Must be treated by an ophthalmologist</i>
Clinical criteria:	<i>Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)</i> <i>AND</i> <i>The condition must be diagnosed by [appropriate diagnostic method – to be finalised]</i> <i>AND</i> <i>Patient must have documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (EDTRS) chart</i>
Definitions <i>(to be finalised at a later stage)</i>	<i>[Visual impairment is defined as best corrected visual acuity using EDTRS charts] - to be finalised.</i>

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<p>Prescriber Instructions</p> <p><i>(to be finalised at a later stage)</i></p>	<p><i>Authority approval for initial treatment of each eye must be sought.</i></p> <p><i>The first authority application for each eye must be made in writing or by telephone.</i></p> <p><i>A written application must include:</i></p> <ul style="list-style-type: none"> <i>a) a completed authority prescription form;</i> <i>b) a completed [insert name of form] - PBS Supporting Information Form; and</i> <i>c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.</i> <p><i>A telephone application must be made following submission by facsimile of a copy of a completed [insert name of form] - PBS Supporting Information Form and a copy of the [appropriate diagnostic report]. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised.</i></p> <p><i>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.</i></p>
<p>Administrative Advice</p> <p><i>(to be finalised at a later stage)</i></p>	<p><i>Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services</i></p> <p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i> <i>Department of Human Services</i> <i>Prior Written Approval of Complex Drugs</i> <i>Reply Paid 9826</i> <i>GPO Box 9826</i> <i>HOBART TAS 7001</i></p> <p><u><i>Note</i></u> <i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><u><i>Note</i></u> <i>No increase in the maximum number of repeats may be authorised</i></p> <p><u><i>Note</i></u> <i>Special Pricing Arrangements apply.</i></p>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT				
aflibercept 4mg/0.1mL injection, 1 x 0.1 ml vial	1	5 2	Eylea	BN
aflibercept 4mg/0.1 mL injection, 1 x 0.09 ml pre-filled syringe	1	5 2	Eylea	BN

Category / Program	<i>GENERAL – General Schedule (Code GE)</i>
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	
Condition:	<i>Macular oedema secondary to central retinal vein occlusion</i>
PBS Indication:	<i>Macular oedema secondary to central retinal vein occlusion</i>
Treatment phase:	<i>Continuing treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<i>Must be treated by an ophthalmologist</i>
Clinical criteria: (To be finalised at a later stage)	<i>Patient must have visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)</i> <i>AND</i> <i>Patient must have previously been granted an authority prescription for the same eye</i>
Prescriber Instructions	<i>(To be finalised at a later stage)</i>
Administrative Advice (To be finalised at a later stage)	<i>Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services</i> <i>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).</i> <u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i> <u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i> <u>Note</u> <i>Special Pricing Arrangements apply.</i>

9 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.

10 Sponsor's Comment

Bayer is concerned that the Pharmaceutical Benefits Advisory Committee's (PBAC) considers a product that has not been approved, formulated or manufactured for use in eye disease in Australia as an appropriate comparator against a Therapeutic Goods Administration (TGA) approved treatment in the reimbursement assessment. For this reason, no formal clinical comparison was undertaken between aflibercept and bevacizumab.