6.01 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 request an Authority Required listing for aflibercept for initial and continuing treatment, by an ophthalmologist, of patients with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO).

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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
AFLIBERCEPT Solution for intravitreal injection, Pre-filled syringe 4 mg/0.1 mL, 1 x 0.09 mL Single-use vial 4 mg/0.1 mL, 1 x 0.1 mL	1	2	$[redacted] (effective price)	Eylea®	BN

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Branch retinal vein occlusion with macular oedema
PBS Indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist.

Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to branched retinal vein occlusion (BRVO), AND Patient must have documented visual impairment defined as a best corrected visual acuity score between 73 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/400), in the eye proposed for treatment, AND The condition must be diagnosed by fluorescein angiography; OR Patient must have a contraindication to fluorescein angiography, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions 1	Authority approval for initial treatment of each eye must be sought.
Prescriber Instructions 2	The first authority application for each eye must be made in writing or by telephone. A written application must include: a) a completed authority prescription form; b) a completed Branched Retinal Vein Occlusion (BRVO) - PBS Supporting Information Form; and c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.
Prescriber Instructions 3	A telephone application must be made following submission by facsimile of a copy of a completed Branched Retinal Vein Occlusion (BRVO) - PBS Supporting Information Form and a copy of the fluorescein angiogram report. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised. 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 or red free photography.

Administrative Advice 1	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). 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 Applications for authority to prescribe should be forwarded to: Department of Human Services ~~Prior Written Approval of~~ Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice 2	The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.
Administrative Advice 3	No increase in the maximum quantity or number of units may be authorised.
Administrative Advice 4	No increase in the maximum number of repeats may be authorised.
Administrative Advice 5	Special Pricing Arrangements apply.
Administrative Advice 6	*Pharmaceutical benefits that have the form aflibercept 0.90 mL pre-filled syringe and pharmaceutical benefits that have the form aflibercept 0.1 mL injection vial are equivalent for the purposes of substitution.*
Cautions	-

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Branch retinal vein occlusion with macular oedema
PBS Indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist.
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for the same eye, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice 1	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).
Administrative Advice 2	No increase in the maximum quantity or number of units may be authorised.
Administrative Advice 3	No increase in the maximum number of repeats may be authorised.
Administrative Advice 4	Special Pricing Arrangements apply.
Administrative Advice 5	Pharmaceutical benefits that have the form aflibercept 0.90 mL pre-filled syringe and pharmaceutical benefits that have the form aflibercept 0.1 mL injection vial are equivalent for the purposes of substitution.
Cautions	-

2.2 The requested effective dispensed price ($[redacted]) was based on an effective ex-manufacturer price of $[redacted]. The associated wholesaler and pharmacist mark-ups ($[redacted]) were calculated from the public ex-manufacturer price ($[redacted]) that was applicable to the June 2015 PBS schedule. Changes to the PBS mark-ups and the public ex-manufacturer price ($[redacted]) after July 2015 would result in a reduced mark-up of $[redacted]. If applied to the submission's proposed effective ex-man price ($[redacted]), this would result in a proposed effective DPMQ of $[redacted].

2.3 A cost minimisation analysis was presented to support the requested listing.

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

3 Background

3.1 TGA status at time of PBAC consideration: This was the first consideration by the PBAC of aflibercept for the treatment of BRVO. The submission was made under TGA/PBAC Parallel Process.

3.2 Aflibercept is approved for the treatment of neovascular (wet) age-related macular degeneration (wet AMD); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO); and diabetic macular oedema (DME). At the time of the evaluation no TGA documentation was available, with the delegate's consideration expected in October 2015. At the time of ESC consideration, aflibercept for the treatment of BRVO had been approved by the TGA on 23 September 2015.

3.3 Aflibercept is currently PBS listed for the treatment of subfoveal choroidal neovascularisation due to age-related macular degeneration (AMD); recommended (March 2012) on a cost-minimisation basis against ranibizumab (aflibercept 2mg ≡ ranibizumab 0.5mg). Aflibercept received a positive PBAC recommendation at the November 2014 PBAC meeting, on a cost-minimisation basis versus ranibizumab, for listing for the treatment of central retinal vein occlusion (CRVO) and diabetic macular oedema (DME), and was subsequently listed for these indications.

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

4 Clinical place for the proposed therapy

4.1 Retinal vein occlusion (RVO) is an obstruction of the veins drawing 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. It is classified into either branch RVO (BRVO) or central RVO (CRVO) based on the site of venous occlusion. The major cause of vision reduction in the acute phase of BRVO is macular oedema due to VEGF-mediated breakdown of the blood-retinal barrier and the increased venous hydrostatic pressure upstream of the venous occlusion. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor, thereby inhibiting the binding and activation of the cognate VEGF receptors.

4.2 The current PBS-listed treatment for BRVO is ranibizumab, so aflibercept is expected to substitute for ranibizumab. Combination therapy with laser therapy may also occur, although this was not considered in the clinical management algorithm presented by the submission. Off-label bevacizumab administered via intravitreal injection may also be replaced in practice.

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

5 Comparator

5.1 The submission nominated ranibizumab as the main comparator. This was agreed to be the appropriate comparator. The submission also nominated laser photocoagulation therapy as a secondary comparator, on the basis that the indirect comparison presented versus ranibizumab requires consideration of aflibercept versus laser therapy. While consideration of the efficacy and safety of aflibercept compared to laser therapy is part of the indirect comparison, the nomination of laser as a secondary comparator was not necessary.

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

6 PBAC consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 With no head-to-head trials comparing aflibercept and ranibizumab available, the submission was based on an indirect comparison using the VIBRANT trial for aflibercept (n=183) and the BRAVO trial for ranibizumab (n=263). Supplementary evidence was provided using two additional ranibizumab trials, Tan 2014 (n=36) and BRIGHTER (n=175).

6.4 Also relevant to the indirect comparison was a published network meta-analysis (Regnier 2015) which included the BRIGHTER trial.

6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Aflibercept		
VIBRANT (24-weeks)	Campochiaro P. A., Clark W. L. et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study.	Ophthalmology.2015, 122(3): 538-544.
VIBRANT (52-weeks)	Clinical study report. A double-masked, randomized, active-controlled study of the efficacy, safety, and tolerability of intravitreal administration of VEGF trap-eye (intravitreal aflibercept injection [IAI]) in patients with macular edema secondary to branch retinal vein occlusion (Week 52).	Regeneron Pharmaceuticals Inc. 2014b
Ranibizumab		
BRAVO (24-week)	Campochiaro P. A., Heier J. S. et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study.	Ophthalmology. 2010, 117(6): 1102-1112 e1101.
BRAVO (52-week)	Brown D. M., Campochiaro P. A. et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study.	Ophthalmology 2011, 118(8): 1594-1602.
BRIGHTER (6-month)	Larsen M., Boscia F. et al. Individually dosed ranibizumab, alone or combined with laser, versus laser alone in branch retinal vein occlusion patients with visual impairment due to macular edema- 6 month results of the BRIGHTER study.	14th EURETINA Congress, London. 2014
	Mones J. Efficacy and safety of ranibizumab 0.5 mg with/without laser versus laser alone in patients with branch retinal vein occlusion: 6-month outcomes from the BRIGHTER study.	Ophthalmologica 232(suppl 2): 1-98.
	Mones J. Evaluation of ranibizumab for macular ischemia in retinal vein occlusion: evidence from the BRIGHTER and CRYSTAL studies.	ARVO Annual Meeting. 2015
	Taylor S., Tadayoni R. et al. Visual acuity outcomes in patients with retinal vein occlusion treated with ranibizumab according to baseline ischaemic status- an analysis of BRIGHTER and CRUISE.	14th EURETINA Congress, London. 2014
	Wickremasinghe S. Efficacy of ranibizumab in branch and central retinal vein occlusion, Outcomes from the BRIGHTER and CRYSTAL studies.	Asia-ARVO, Yokohama. 2015
	Samantha Fraser-Bell, Ranibizumab, alone or combined with laser, versus laser alone in eyes with branch retinal vein occlusion with visual impairment due to macular oedema: 6 month results of the BRIGHTER study.	Requested from author
Tan 2014	Tan M. H., McAllister I. L. et al. Randomized controlled trial of intravitreal ranibizumab versus standard grid laser for macular edema following branch retinal vein occlusion.	Am J Ophthalmol 2014 157(1): 237-247 e231.
Systematic review/Meta-analysis of direct randomised trials		
Regnier 2014	Regnier S. and Bezlyak V. Efficacy of treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis.	ISPOR 17th Annual European Congress, Amsterdam. 2014 17(7): A604.
Regnier 2015	Regnier S. A., Larsen M. et al. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis.	BMJ Open 2015, 5(6): e007527.

Source: Table B.2.2 of the submission and modified during the evaluation.

6.6 The key features of the randomised trials included in the indirect comparison are summarised in Table 2 below.

Table 2: Summary of trials used in the indirect comparison

Trial ID	Trial design	Primary outcome	Aflibercept	Common reference	Ranibizumab	Used in the CMA
Main analyses						
VIBRANT	P3, MC, R, DM, AC, 52 weeks^	Proportion of subjects who gained ≥15 letters in BCVA at week 24 from baseline	AFB 2mg IVT 2Q4 from baseline to month 6, then 2Q8 to week 48 (n=91)	Grid laser at baseline, rescue laser PRN at weeks 12, 16 & 20 (n=92)	NA	Yes[#]
BRAVO	P3, MC, R, AC, DM, 12mth*	Mean change from baseline BCVA at month 6	NA	Rescue laser PRN from month 3 onwards (n=132)	RBZ 0.5mg IVT 2Q4: baseline to month 6 then PRN (n=131)	Yes[#]
Supplementary analyses						
BRIGHT-ER[‡]	Ongoing, P3b, OL, R, AC, 24mth	Mean change from baseline BCVA at month 6		Rescue laser PRN at investigator discretion (n=92)	RBZ 0.5mg IVT 2Q4: baseline to month 3, then PRN (n=183)	Sensitivity analysis
Tan 2014	R, Masked, SIC, 12mth	Mean change from baseline BCVA at month 12		Laser PRN at week 13 and 25 (n=21)	RBZ 0.5mg IVT 2Q4: baseline to month 6 the PRN (n=15)	Sensitivity analysis

^ VIBRANT: Following month 6, patients in the laser arm became eligible for rescue treatment with aflibercept, and received 3 initial 2mg IVT injections given 2Q4, followed by 2mg IVT 2Q8 up to week 48.
* BRAVO: After 6 months, all patients with a BCVA ≤20/40 or CST ≥ 250μm received ranibizumab.
‡ BRIGHTER: The submission does not include the Ranibizumab + Laser treatment arm in the clinical evaluation.
# Mean number of injections at 6 months: adjusted for 3 loading doses (VIBRANT); unadjusted (BRAVO).
Abbreviations: 2Q4 = every month; 2Q8 = every 2 months; AC = active controlled, AFB = aflibercept; DM = double masked; IVT = intravitreal; MC = multicentre; mth = month; NA = not applicable; OL = open label; P3 = phase 3; PRN = as required; R = randomised; RBZ = ranibizumab; SIC = sham injection controlled. Source: Table B.2.5, pp63-65 of the submission.

6.7 The Regnier 2015 publication was an update to the systematic review by Glanville (2014). Of particular interest was the inclusion of Bayesian network meta-analyses, where the results from BRAVO are considered with the context of a comparison with sham injection. Given the inconsistency in approach to the administration of laser treatment in the comparator arms of the ranibizumab and aflibercept trials (laser on Day 1 in VIBRANT; rescue laser in BRAVO and Tan 2014 and at investigator discretion in BRIGHTER), such alternative analyses were informative (see 'Comparative effectiveness' below).

Comparative effectiveness

6.8 Table 3 provides the results of the indirect comparison of aflibercept and ranibizumab for the proportion of patients who gained/lost ≥15 letters from baseline BCVA at 6 and 12 months and Table 4 provides the results for mean change in best corrected visual acuity (BCVA) in ETDRS letter score.

Table 3: Summary of results for the indirect comparison: proportion of patients who gained/lost ≥15 letters from baseline BCVA at 6 and 12 months (VIBRANT, BRAVO)

Trial	Gained ≥15 letters		Lost ≥15 letters		Gained ≥15 letters		Lost ≥15 letters	
	AFB/RBZ	Laser	AFB/RBZ	Laser	AFB/RBZ vs laser		AFB/RBZ vs laser	
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	RR (95% CI)	RD% (95% CI)	RR (95% CI)	RD% (95% CI)
Month 6								
VIBRANT	48/91 (52.7)	24/90 (26.7)	0/91 (0)	4/90 (4.4)	1.98 (1.33, 2.93)	26.1 (12.3, 39.8)	0.11 (0.01, 2.01)	-4.4 (-9.2, 0.3)
BRAVO	80/131 (61.1)	38/132 (28.8)	2/131 (1.5)	6/132 (4.5)	2.12 (1.57, 2.87)	32.3 (20.9, 43.7)	0.34 (0.07, 1.63)	-3.0 (-7.2, 1.1)
Indirect comparison: AFB vs RBZ					0.93 (0.57, 1.53)	-6.2 (-24.0, 11.6)	NC^	-1.4 (-7.4, 1.1)
Month 12								
VIBRANT	52/91 (57.1)	37/90 (41.1)	2/91 (2.2)	1/90 (1.1)	1.39 (1.02, 1.88)	16.0 (1.7, 30.4)	1.98 (0.18, 21.43)	1.1 (-2.6, 4.8)
BRAVO	79/131 (60.3)	58/132 (43.9)	3/131 (2.3)	8/132 (6.1)	1.37 (1.08, 1.74)	16.4 (4.5, 28.3)	0.38 (0.10, 1.39)	-3.8 (-8.6, 1.0)
Indirect comparison: AFB vs RBZ					1.01 (0.69, 1.49)	-0.3 (-19.0, 18.3)	5.23 (0.35, 79.19)	4.9 (-1.2, 10.9)

Results in bold indicate RRs or RDs that are statistically significant.

^ *Applying the point estimates and 95% CIs to Bucher's method: RR = 0.33, 95% CI: 0.01, 8.96.*

Abbreviations: AFB = aflibercept; CI = confidence interval; NC = not calculable; RBZ = ranibizumab; RD = risk difference; RR = relative risk. Source: Table B.6.1, p 118 and B.6.4, p128 of the submission.

Table 4: Summary of results for the indirect comparison: mean change in baseline BCVA in ETDRS letter score at 6 and 12 months (VIBRANT, BRAVO)

		VIBRANT		BRAVO	
		AFB (n=91)	**Laser (n=90)**	**RBZ (n=131)**	Laser (n=132)
Month 6					
Baseline	Mean; SD	58.6	57.7	53.0 (12.5)	54.7 (12.2)
Month 6		75.6	64.6	NR	NR
Δ b/line to month 6		17.0 (11.88)	6.9 (12.91)	18.3 (13.2)	7.3 (13.0)
AFB/RBZ vs laser	Adjusted	**10.5 (7.1, 14.0)**		**11.0 (7.8, 14.2)**	
Indirect comparison	MD^; 95% CI	AFB vs RBZ: -0.50 (-5.24, 4.24)			
Month 12					
Baseline	Mean; SD	58.6	57.7	53.0 (12.5)	54.7 (12.2)
Month 12		75.7	69.9	NR	NR
Δ b/line to month 12*		17.1 (13.07)	12.2 (11.94)	18.3 (14.6)	12.1 (14.4)
AFB/RBZ vs laser	Adjusted	**5.2 (1.7, 8.7)**		**6.2 (2.7, 9.8)**	
Indirect comparison	MD^; 95% CI	AFB vs RBZ: -1.00 (-6.02, 4.02)			

Results in bold indicate results that are statistically significant.

^ Adjusted mean difference: VIBRANT – analysis of covariance with baseline measurement as covariate and treatment group, region and baseline BCVA as fixed factors; BRAVO – based on pairwise analysis of variance models adjusted for baseline ETDRS letter score.

* Crossover to VEGF treatment in the laser treatment arm: VIBRANT: 67 patients (74%) received aflibercept as rescue therapy from week 24 (6 months); BRAVO: 87.1% of patients received ranibizumab rescue treatment from week 24 (6 months).

Abbreviations: AFB = aflibercept; CI = confidence interval; MD = mean difference; NR = not reported; RBZ = ranibizumab; SD = standard deviation. Source: Table B.6.2, p126 of the submission.

6.9 The results of the indirect comparison indicated there was no statistically significant difference between aflibercept and ranibizumab for proportion of patients who gained/lost ≥15 letters from baseline BCVA at 6 and 12 months.

6.10 The results of the indirect comparison indicated there was no statistically significant difference between aflibercept and ranibizumab for mean change from baseline BCVA in ETDRS letter score at 6 and 12 months. Point estimates and the 95% confidence intervals for the 6 and 12 month analyses did not exceed the 10 letter

difference the PBAC considered to be clinically meaningful (ranibizumab DME PSD, November 2013).

6.11 Table 5 provides results from the indirect comparison of aflibercept and ranibizumab using data from BRAVO following a patient cohort adjustment for the eligibility criteria from VIBRANT, as reported in Regnier 2015 as well as results from the network meta-analyses in Regnier 2015.

Table 5: Summary of the results from Regnier 2015

Post-hoc adjustment of results from BRAVO^	**VIBRANT**	**BRAVO^**	**AFB vs RBZ**
Mean change from baseline BCVA in ETDRS score (letters)	AFB: 17.0, SD = 11.9 Laser: 6.9, SD = 12.9	RBZ: 18.1, SD = 13.2 Laser: 7.3, SD = 13.1	MD = -0.30 95% CI: -5.18, 4.58
Proportion of patients who gain ≥15 letters from baseline	AFB: 48/91 (53%) Laser: 24/90 (27%)	RBZ: 77/129 (60%) Laser: 38/131 (29%)	RD% = -4.6, 95% CI: -22.5, 13.3
Network meta-analysis	**AFB vs laser**	**RBZ vs laser**	**AFB vs RBZ**
Mean change from baseline BCVA in ETDRS score (letters)	11.5 95% CI: 7.5, 15.9	10.2 95% CI: 4.6, 15.5	MD = -1.4 95% CI: -8.5, 5.2
Proportion of patients who gain ≥15 letters from baseline	AFB: 39% probability	RBZ: 35% probability	OR = 0.95 95% CI: 0.11, 6.17
	Laser: <1% probability		

^ Patient level data from BRAVO was re-analysed to match key eligibility criteria from VIBRANT (i.e. criteria relating to BCVA, duration of disease at baseline). Specifically, patients were excluded from the analysis if they had a baseline BCVA of <24 letters or duration of disease of more than 12 months.

Abbreviations: AFB = aflibercept; BCVA = best corrected visual acuity; CI = confidence interval; MD = mean difference; NR = not reported; OR = odds ratio; RBZ = ranibizumab. Source: Table B.6.8, p134 of the submission.

6.12 Across the analyses presented in Regnier 2015, there were no statistically significant differences between aflibercept and ranibizumab for mean change from baseline BCVA in ETDRS letter score and the proportion of patients who gain ≥15 letters from baseline at 6 months.

6.13 A summary of supplementary analyses for the indirect comparisons including BRIGHTER and Tan 2014 are presented in Table 6 below. No statistically significant differences were observed across the indirect comparisons.

Table 6: Summary of the supplementary analyses: indirect comparisons including BRIGHTER and Tan 2014

Indirect comparison	Patients who gained ≥15 letters		Patients who lost ≥15 letters	
	RR (95% CI)	RD% (95% CI)	RR (95% CI)	RD% (95% CI)
VIBRANT vs BRAVO + BRIGHTER – Month 6	0.96 (0.50, 1.85)	-2.6 (-18.8, 13.6)	NA	
VIBRANT vs BRAVO + Tan 2014 – Month 12	0.84 (0.27, 2.60)	-3.7 (-23.5, 16.2)	5.99 (0.53, 67.55)	10.7 (-7.5, 28.9)
	Mean change from baseline BCVA in ETDRS letter score, MD (95% CI)			
VIBRANT vs BRAVO + BRIGHTER – Month 6	0.57 (-3.60, 4.74)			
VIBRANT vs BRAVO + Tan 2014 – Month 12	-2.58 (-9.70, 4.54)			
	Mean change from baseline CRT, Unadjusted MD (95% CI)			
VIBRANT vs BRAVO + Tan 2014 – Month 12	64.99 (-42.95, 172.93)			

Abbreviations: BCVA = best corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; MD = mean difference; RD = risk difference; RR = relative risk.
Source: Table B.6.1, p118; Table B.6.2, p126; Table B.6.3, p127 and Table B.6.4, p128 of the submission.

6.14 Overall, the indirect comparisons presented by the submission demonstrated no statistically significant differences between aflibercept and ranibizumab.

Comparative harms

6.15 The submission provided detailed safety outcomes from the VIBRANT, BRAVO and Tan 2014 trials, but did not provide any statistical comparisons of safety data. The submission stated that the safety profile of aflibercept in VIBRANT was as expected and in line with previously reported safety data for other indications. Statistical analyses of the available 6 month safety data for VIBRANT and BRAVO were conducted during the evaluation. Results of the indirect comparison are presented in Table 7 below. These results should be interpreted with caution, given the wide degree of variability in adverse event rates in the laser common comparator arms (e.g. serious adverse events - VIBRANT: 9.8%; BRAVO: 4.6%; conjunctival haemorrhage – VIBRANT: 4.3%; BRAVO: 42.0%).

Table 7: Results of the statistical comparison of key adverse events

	VIBRANT		BRAVO		Indirect comparison: AFB vs RBZ	
	RR (95% CI)	RD%(95% CI)	RR (95% CI)	RD%(95% CI)	RR (95% CI)	RD%(95% CI)
Non-ocular SAE	0.90 (0.36, 2.23)	-1.0 (-9.4, 7.4)	5.04 (0.60, 42.54)	3.1 (-0.5, 6.7)	0.18 (0.02, 1.81)	-4.1 (-13.2, 5.1)
Any SAE	1.01 (0.42, 2.43)	0.1 (-8.5, 8.7)	2.35 (0.93, 5.93)	6.2 (-0.2, 12.6)	0.43 (0.12, 1.54)	-6.1 (-16.8, 4.7)
Conjunctival haemorrhage	**4.55 (1.60, 12.92)**	**15.4 (6.2, 24.6)**	**1.30 (1.01, 1.68)**	**12.6 (0.6, 24.7)**	**3.50 (1.19, 10.24)**	2.8 (-12.3, 17.9)
Eye pain	0.81 (0.22, 2.92)	-1.0 (-7.3, 5.2)	1.11 (0.62, 1.97)	1.7 (-7.1, 10.4)	0.73 (0.18, 2.96)	-2.7 (-13.4, 8.1)
Eye irritation	4.04 (0.46, 35.49)	3.3 (-1.4, 8.0)	0.81 (0.33, 1.98)	-1.5 (-7.6, 4.7)	5.02 (0.48, 52.61)	4.8 (-3.0, 12.5)
Cataract	5.05 (0.25, 103.85)	2.2 (-1.4, 5.8)	1.01 (0.26, 3.94)	0.0 (-4.2, 4.2)	5.02 (0.18, 138.24)	2.2 (-3.4, 7.7)
Retinal vascular disorder	0.34 (0.01, 8.16)	-1.1 (-4.1, 1.9)	1.68 (0.76, 3.70)	4.7 (-2.3, 11.7)	0.20 (0.01, 5.35)	-5.8 (-13.4, 1.8)
Retinal exudates	0.34 (0.01, 8.16)	-1.1 (-4.1, 1.9)	1.61 (0.97, 2.67)	9.3 (-0.3, 19.0)	0.21 (0.01, 5.27)	**-10.4 (-20.5, -0.4)**
Vitreous haemorrhage	0.34 (0.01, 8.16)	-1.1 (-4.1, 1.9)	0.34 (0.07, 1.63)	-3.0 (-7.2, 1.1)	1.00 (0.03, 35.22)	2.0 (-3.2, 7.1)

Note: RR and RD were estimated during the evaluation using StatsDirect Version 2.78. Indirect comparison utilised methods consistent with Bucher 1997. Results in bold indicate RRs or RDs that are statistically significant.

Source: Constructed during the evaluation

6.16 With the exception of conjunctival haemorrhage (relative risk only), there were no significant differences between aflibercept and ranibizumab for any key safety outcomes.

Comparative benefit/harms

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

Table 8: Summary of comparative benefits and harms for aflibercept and ranibizumab

Benefits							
Proportion of patients who gained ≥15 letters in BCVA at 6 months							
	AFB or RZB vs laser			**Indirect comparison: AFB vs RBZ**			
	N	**RR (95% CI)**	**RD (95% CI)**	**RR (95% CI)**		**RD (95% CI)**	
VIBRANT	181	1.98 (1.33, 2.93)	26.1 (12.3, 39.8)	0.93 (0.57, 1.53)		-6.2 (-24.0, 11.6)	
BRAVO	263	2.12 (1.57, 2.87)	32.3 (20.9, 43.7)				
Proportion of patients who lost ≥15 letters in BCVA at 6 months							
	N	**RR (95% CI)**	**RD (95% CI)**	**RR (95% CI)**		**RD (95% CI)**	
VIBRANT	181	0.11 (0.01, 2.01)	-4.4 (-9.2, 0.3)	NC^		-1.4 (-7.4, 1.1)	
BRAVO	263	0.34 (0.07, 1.63)	-3.0 (-7.2, 1.1)				
Harms							
Trial	**AFB**	**Laser**	**RBZ**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
					AFB	**Laser**	**RBZ**
Conjunctival haemorrhage							
VIBRANT	18/91	4/92	-	***4.55 (1.60, 12.92)***	19.8	4.3	-
BRAVO	-	55/131	71/130	***1.30 (1.01, 1.68)***	-	42.0	54.6
Indirect comparison: AFB vs RBZ				***3.50 (1.19, 10.24)***	-		
Any SAE							
VIBRANT	9/91	9/92	-	*1.01 (0.42, 2.43)*	9.9	9.8	-
BRAVO	-	6/131	14/130	*2.35 (0.93, 5.93)*	-	4.6	10.8
Indirect comparison: AFB vs RBZ				*0.43 (0.12, 1.54)*	-		

Results in bold indicate RRs or RDs that are statistically significant.

^ *Applying the point estimates and 95% CIs to Bucher's method: RR = 0.33, 95% CI: 0.01, 8.96.*

Abbreviations: AFB = aflibercept; CI = confidence interval; NC = not calculable; RBZ = ranibizumab; RD = risk difference; RR = relative risk; SAE = serious adverse event. Source: Compiled during the evaluation.

6.18 On the basis of the indirect evidence presented by the submission, patients treated for 6 months with aflibercept in comparison to ranibizumab:

- would be equally likely to gain or lose at least 15 letters in best corrected visual acuity (BCVA)
- would potentially be up to 3.5 times more likely to have experienced conjunctival haemorrhage
- would be equally likely to experience serious adverse events (SAEs).

Clinical claim

6.19 The submission claimed that, for patients with macular oedema secondary to BRVO, aflibercept is non-inferior to ranibizumab and superior to laser photocoagulation in efficacy. The efficacy claim versus both ranibizumab and laser is adequately supported for the outcomes of mean change in BCVA in ETDRS letter score and the proportion of patients with a gain of ≥15 letters from baseline to month 6. Although

there were issues associated with the exchangeability of the VIBRANT and BRAVO trials (inconsistencies in the laser comparator arms, duration of disease, ETDRS inclusion criteria), additional published analyses utilising a matched patient cohort and network meta-analyses (Regnier 2015) resulted in similar estimates to the indirect comparisons presented in the submission.

6.20 The submission claimed that aflibercept is non-inferior in safety compared with ranibizumab and laser photocoagulation. While the limited reporting of safety data in the ranibizumab trials and differences in common comparator event rates were of consequence to the reliability of the indirect comparison, it was considered that the adverse event profiles for ranibizumab and aflibercept were similar. For the comparison of aflibercept and laser photocoagulation (VIBRANT) insignificant differences in adverse events (with the exception of conjunctival haemorrhage) adequately supported the submission's claim of non-inferiority over the 6 month head-to-head trial period. Long-term comparative safety in BRVO has yet to be demonstrated.

6.21 The PBAC considered that the claim of non-inferior comparative effectiveness and comparative safety against ranibizumab was reasonable.

Economic analysis

6.22 The submission presented a cost-minimisation analysis (CMA) based on the indirect comparison of aflibercept and the main comparator ranibizumab and a cost-effectiveness analysis comparing costs and outcomes of aflibercept vs laser treatment. Since laser treatment was not a relevant comparator, the modelled cost-effectiveness analysis was not evaluated.

6.23 The equi-effective doses and cost calculations were conducted with respect to 24 weeks and 52 weeks. In the base case 24 week analysis, the average dose per patient for aflibercept was adjusted to correspond to the draft of PI (pending TGA approval at the time of evaluation), which involved a reduction from six (as per the aflibercept arm of VIBRANT) to three loading doses. The mean number of doses per patient treated with aflibercept was estimated on the basis of an unsupported assumption that the frequency of re-injection after three initial loading doses (between week 12 and week 24) would be equivalent to the frequency that was observed in the aflibercept arm of the VIBRANT trial between week 24 and week 52. The mean number of doses per patient for ranibizumab was directly derived from the BRAVO trial, where six loading doses were used (consistent with the approved PI for ranibizumab). The ESC noted that a regimen of three initial loading doses was accepted by the TGA.

6.24 Table 9 summarises the comparison of treatment doses of aflibercept and ranibizumab and corresponding dose relativities presented by submission estimated from VIBRANT and BRAVO. During the evaluation an additional analysis involving unadjusted aflibercept mean injection numbers over 12 months was conducted.

Table: 9: Calculation of equi-effective doses for aflibercept and ranibizumab (VIBRANT and BRAVO)

Treatment period		AFB		RBZ
		Adjusted for draft PI	Unadjusted	
Week 1-12		3.00 (draft PI)	5.66 (VIBRANT)	5.69 (BRAVO^)
Week 13- 24		1.44 (VIBRANT: dose frequency from the end of 24th - end of the 52nd week)		
Week 25-52		3.35 (VIBRANT)	3.35 (VIBRANT)	2.69 (BRAVO^)
Total doses	Week 1-24	4.44	5.66	5.69
	Week 1-52	7.79	9.01	8.38
Dose relativity: AFB:RBZ				
Adjusted (base case)	Week 1-24	**4.44: 5.69 = 1: 1.28**		
Unadjusted		5.66: 5.69 = 1: 1.01		
Adjusted	Week 1-52	7.79: 8.38 = 1: 1.08		
Unadjusted		*9.01: 8.38 = 1: 0.93*		

^ Summary of the BRAVO study reported by the Pharmaceuticals and Medical Devices Agency, Japan: 745 injections were received at month 6 and 1,098 injections were received by month 12 among the 130 patients in the ranibizumab arm of the safety analysis set.

Abbreviations: AFB = aflibercept; RBZ = ranibizumab. Source: Table D.1.1, p177 of the submission.

6.25 There is no clinical evidence to support the assumption that the protocol-determined frequency of re-injections between week 24 and 52 in the VIBRANT trial would be consistent with the "treat and extend" clinical practices of re-injections between weeks 12 and 24. The recommended "treat and extend" clinical practice depends on the visual and anatomic outcomes. Furthermore, there was no evidence to demonstrate that patients at 12 weeks would respond to an ongoing 8 weekly regimen in a similar way as patients after 24 weeks. However, as noted in the 12 week outcomes for the comparison vs laser, there was a clinically significant impact on BCVA (adjusted mean difference: 10.10 letters, 95% CI: 4.27, 11.30). On balance, there still remains the possibility that patients may continue to receive monthly injections to 24 weeks.

6.26 Table 10 summarises the results of the base case CMA which is calculated from the 24 week dose relativity incorporating adjusted aflibercept utilisation from VIBRANT and ranibizumab utilisation directly from BRAVO.

6.27 The CMA presented in the submission, includes the cost of drugs, drug administration, and also the cost of rescue laser. Price parity was applied for calculation of drug costs (updated during the evaluation to account for the July 2015 public DPMQ price for ranibizumab, $1380.36) with associated administration fees per injection (MBS item 42740: $300.75) and laser treatment (MBS item $451.40). In the base case CMA, the cost of laser treatment for the first 6 months applied only to the ranibizumab treatment reflecting the differences in the designs of the RCTs: no rescue laser treatment were allowed in the aflibercept arm of the VIBRANT trial up to week 24, while a single rescue laser treatment was allowed in ranibizumab arm of the BRAVO trial starting from month 3. It is unlikely that laser treatment will be exclusively associated with ranibizumab treatment in clinical practice. The inclusion of the laser treatment cost favours aflibercept over ranibizumab in the CMA.

Table 10: CMA of aflibercept and ranibizumab at 24 weeks (base case)

	AFB (VIBRANT: adjusted for PI)	RBZ (BRAVO)	Difference
Mean injections	4.44	5.69	-
Drug cost (mean injections × $1,380.36)*	$	*$7,850*	-$
Drug administration cost (mean injections × $300.75)	$	$1,710	-$
Rescue laser treatments	0.00	0.21	-
Laser cost (mean rescue laser treatments × $451.10)	$0	$96	-$
Total cost*	***$***	***$9,657***	***-$***
Excluding cost of laser treatment*	***$***	***$9,561***	***-$***

* Updated according to the July 2015 public DPMQ for ranibizumab ($1380.36).
Abbreviations: AFB = aflibercept; RBZ = ranibizumab. Source: Table D.2.3, p179 of the submission

6.28 Sensitivity analyses incorporating alternative dose relativities for aflibercept: ranibizumab are presented in Table 11.

Table 11: Sensitivity analyses for the CMA of aflibercept and ranibizumab

		AFB:RBZ dose relativity	Total cost*		
			AFB	RBZ	Difference
Week 1-24	**Base case: VIBRANT (adjusted): BRAVO**	**1: 1.28**	***$***	***$9,657***	***-$***
	VIBRANT (unadjusted): BRAVO	1: 1.01	*$*	*$9,657*	*-$*
	VIBRANT (adjusted): BRAVO + BRIGHTER	1: 1.18	*$*	*$8,881*	*-$*
Week 1-52^	VIBRANT (adjusted): BRAVO	1: 1.08	*$*	*$14,294*	*-$*
	VIBRANT (unadjusted): BRAVO	*1: 0.93*	*$*	*$14,294*	*$*
	VIBRANT (adjusted): BRAVO + Tan 2014	1: 1.07	*$*	*$14,232*	*-$*
	Aflibercept CRVO submission: November 2014	1: 1.22	*$*	*$14,294*	*-$*

* Updated according to the July 2015 public DPMQ for ranibizumab ($1380.36).
^ Laser utilisation in the Week 1-52 week analysis for aflibercept was 0.1 (VIBRANT) and depending on the sensitivity analyses, 0.45 (BRAVO) or 0.41 (Weighted between BRAVO + Tan 2014) for ranibizumab. For the Week 1-24 analysis, laser utilisation for aflibercept was 0 and 0.21 for ranibizumab. Laser utilisation was not reported in BRIGHTER.
Abbreviations: AFB = aflibercept; RBZ = ranibizumab.
Source: Table D.2.4, Table D.2.5, Table D.2.6, Table D.2.7 and Table D.2.8, pp180-182 of the submission.

6.29 Results of the CMA are sensitive to the assumptions about the mean number of equi-effective doses but not sensitive to the differences in frequency of laser treatment between aflibercept and ranibizumab. Depending on the number of loading doses in the aflibercept regimen, cost savings associated with aflibercept at 24 weeks vary from $ per patient (base case analysis) to $ per patient and are reduced to $ per patient if cost of laser is excluded (VIBRANT unadjusted utilisation). Results of CMA at 52 weeks indicate that costs range from a savings associated with aflibercept of $ per patient (VIBRANT adjusted utilisation), to an additional cost of $ per patient (VIBRANT unadjusted utilisation) in comparison to ranibizumab (BRAVO).

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

Drug cost/patient/year $[redacted]

6.30 Based on the adjusted mean number of injections in the VIBRANT trial (3 loading doses; 7.79) and the effective price, the cost of drug per patient per year was $[redacted]. The submission presented a cost of $[redacted], using the public DPMQ. If the unadjusted mean number of doses from VIBRANT was used (9.01 injections), the cost per patient per year increased to $[redacted].

Estimated PBS usage & financial implications

6.31 This submission was not considered by DUSC. The submission used a combination of an epidemiological and market approach to estimate the financial implications for the requested listing of aflibercept for BRVO, given the recent availability of ranibizumab on the PBS (1 July 2015).

Table 12: Estimated financial implications for the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Eyes treated	1247	1420	1582	1769	1948
Number of AFB injections	9716	13,753	16,398	18,697	20,811
AFB scripts	9716	13,753	16,398	18,697	20,811
Net cost* to PBS - AFB	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in RBZ scripts	-10,452	-14,590	-17,331	-19,741	-21,961
Savings to PBS for less RBZ use	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**
Net cost to PBS – AFB injections based on VIBRANT (9.01 in year 1) and co-payments equal between AFB and RBZ	*$[redacted]*	*$[redacted]*	*$[redacted]*	*$[redacted]*	*$[redacted]*

*The submission has identified net cost to PBS (i.e. PBS cost less co-payments) as cost to Government. This does not include other government costs such as costs to MBS.
Abbreviations: AFB = aflibercept; RBZ = ranibizumab. Source: Table E.4.1, p195 of the submission.

The redacted table above shows that the number of patients treated with aflibercept for BRVO is estimated to be less than 10,000 per year at a net saving to the PBS of less than $10 million per year.

6.32 The submission estimated savings to the PBS of $[redacted] in year 1 increasing to $[redacted] in year 5. These estimated savings relied on the assumption that patients using aflibercept would require fewer injections in the first year of treatment (7.79) than those treated with ranibizumab (8.38 injections in year 1).

6.33 The submission also assumed different co-payment levels for aflibercept and ranibizumab patients. With a higher weighted co-payment level for aflibercept ($10.62) compared to ranibizumab ($9.59), this resulted in greater savings than would be realised if co-payments were the same.

6.34 Based on evidence from the VIBRANT trial, which indicated that patients would use 9.01 injections in the first year of treatment, and assuming a weighted co-payment of $10.12 across all patients, the cost-minimisation analysis estimated net costs to the PBS of $[redacted] in year 1, increasing to $[redacted] in year 5. The estimated financial implications depended on the assumed number of injections. If injection numbers in year 1 were assumed to be the same for aflibercept and ranibizumab, then there would be no expected cost to the PBS.

Financial Management – Risk Sharing Arrangements

6.35 The submission stated the sponsor is aware a risk sharing arrangement (RSA) is in place for ranibizumab and it was anticipated that a corresponding RSA would be required for aflibercept following a positive PBAC recommendation. The submission provided no further detail on a potential RSA, but it did indicate that the sponsor was willing to collaborate with the Department to implement an RSA for aflibercept in BRVO.

6.36 The PBAC noted that there is an existing RSA for aflibercept for CRVO indications, and ranibizumab for macular oedema secondary to retinal vein occlusion (RVO) indications. The PBAC agreed that aflibercept for BRVO should be included in the existing RSA and that there should be no increase in the joint caps shared with ranibizumab.

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 secondary to branched retinal vein occlusion (BRVO). 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 existing administrative arrangements for ranibizumab in BRVO.

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 and 0.5 mg ranibizumab injection.

7.3 The PBAC noted that the requested restriction, maximum quantity and repeats for aflibercept for BRVO are identical to that for ranibizumab.

7.4 The PBAC noted that the clinical place for aflibercept is as an alternative to ranibizumab for the treatment of BRVO.

7.5 The PBAC accepted ranibizumab as appropriate comparator.

7.6 On the basis of the indirect evidence using laser photocoagulation as the common reference, there appears to be no difference in benefits and harms between aflibercept and ranibizumab.

7.7 The PBAC considered the issues raised in the Commentary with regards to the trial (VIBRANT) using six initial loading doses versus the regimen of three initial loading doses proposed for the TGA product information. The PBAC considered that given the TGA had since accepted the regimen of three initial loading doses, it was reasonable to accept this.

7.8 The PBAC considered the issues in the cost-minimisation analysis between aflibercept and ranibizumab, as reported in paragraphs 6.23 to 6.25. The PBAC recalled its November 2014 consideration of aflibercept for macular oedema secondary to central retinal vein occlusion (CRVO) where it recommended a 1:1 dose relativity to ranibizumab (aflibercept CRVO PSD, November 2014). The PBAC agreed that a 1:1 dose relativity should also apply to the BRVO indication. The PBAC noted that in its Pre-PBAC Response, the sponsor is again willing to accept a 1:1 dose relativity (price parity) to ranibizumab.

7.9 The PBAC advised that aflibercept is not suitable for prescribing by nurse practitioners.

7.10 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:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT Solution for intravitreal injection, Pre-filled syringe 4 mg/0.1 mL, 1 x 0.09 mL Single-use vial 4 mg/0.1 mL, 1 x 0.1 mL	1	2	Eylea®	BN

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Branch retinal vein occlusion with macular oedema
PBS Indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Initial treatment

Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by an ophthalmologist.
Clinical criteria:	Patient must have visual impairment due to macular oedema secondary to branched retinal vein occlusion (BRVO), AND Patient must have documented visual impairment defined as a best corrected visual acuity score between 73 and 20 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 metres (approximate Snellen equivalent 20/40 to 20/400), in the eye proposed for treatment, AND The condition must be diagnosed by fluorescein angiography; OR Patient must have a contraindication to fluorescein angiography, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions 1	Authority approval for initial treatment of each eye must be sought.
Prescriber Instructions 2	The first authority application for each eye must be made in writing or by telephone. A written application must include: a) a completed authority prescription form; b) a completed Branched Retinal Vein Occlusion (BRVO) - PBS Supporting Information Form; and c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.

Prescriber Instructions 3	A telephone application must be made following submission by facsimile of a copy of a completed Branched Retinal Vein Occlusion (BRVO) - PBS Supporting Information Form and a copy of the fluorescein angiogram report. The original documentation must be submitted to the Chief Executive Medicare by post after the application has been authorised. 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 or red free photography.
Administrative Advice 1	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). 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 Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice 2	The first authority application may be faxed to the Department of Human Services on 1300 093 177 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The Department will then contact the prescriber by telephone.
Administrative Advice 3	No increase in the maximum quantity or number of units may be authorised.
Administrative Advice 4	No increase in the maximum number of repeats may be authorised.
Administrative Advice 5	Special Pricing Arrangements apply.
Administrative Advice 6	Pharmaceutical benefits that have the form aflibercept 0.90 mL pre-filled syringe and pharmaceutical benefits that have the form aflibercept 0.1 mL injection vial are equivalent for the purposes of substitution.
Cautions	-

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Branch retinal vein occlusion with macular oedema
PBS Indication:	Branch retinal vein occlusion with macular oedema
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by an ophthalmologist.
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for the same eye, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice 1	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).
Administrative Advice 2	No increase in the maximum quantity or number of units may be authorised.
Administrative Advice 3	No increase in the maximum number of repeats may be authorised.
Administrative Advice 4	Special Pricing Arrangements apply.
Administrative Advice 5	Pharmaceutical benefits that have the form aflibercept 0.90 mL pre-filled syringe and pharmaceutical benefits that have the form aflibercept 0.1 mL injection vial are equivalent for the purposes of substitution.
Cautions	-

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 welcomes the recommendation of the PBAC.