6.2 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 (for treatment of subfoveal choroidal neovascularisation due to age-related macular degeneration) to include treatment of a patient with visual impairment due to diabetic macular oedema (DME).

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	Proprietary Name and Manufacturer	
AFLIBERCEPT				
aflibercept 4mg/0.1mL injection, 1 x 0.1 mL vial	1		Eylea	BN
aflibercept 4mg/0.1mL injection, 1 x 0.09 mL pre-filled syringe	1		Eylea	BN

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	
Severity:	
Condition:	Diabetic macular oedema
PBS Indication:	Diabetic 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: *(to be finalised at a later stage)*	The condition must be due to diabetic macular oedema AND The condition must be diagnosed by fluorescein angiography *AND* *Patient must have documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (EDTRS) chart* *AND* *The treatment must be as monotherapy; OR* *The treatment must be in combination with laser photocoagulation*
Definitions	*Visual impairment is defined as best corrected visual acuity score between 73 and 24 letters based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts administered at a distance of 4 meters (approximate Snellen equivalent 20/40-20/320).*
Prescriber Instructions *(to be finalised at a later stage)*	*Treatment must be monthly injections for up to five months followed by 2 mg doses every eight weeks.* *Authority approval for initial treatment of each eye must be sought.* *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 [insert name of form] - PBS Supporting Information Form; and* *c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.* *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.* *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.*

Administrative Advice	*Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services* *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* *Written applications for authority prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *GPO Box 9826* *HOBART TAS 7001* *Note* *No increase in the maximum quantity or number of units may be authorised* *Note* *No increase in the maximum number of repeats may be authorised* *Note* *Special Pricing Arrangements apply.*

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	
Severity:	
Condition:	Diabetic macular oedema
PBS Indication:	Diabetic 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: *(to be finalised at a later stage)*	The condition must be due to diabetic macular oedema AND The treatment must be as monotherapy; *OR* *The treatment must be in combination with laser photocoagulation* AND Patient must have previously been granted an authority prescription for the same eye
Prescriber instructions *(to be finalised at a later stage)*	*Treatment should be administered every eight weeks and continued until maximum visual acuity is achieved, confirmed by stable visual acuity. Treatment must be ceased when stable visual acuity is achieved.* [Stable visual acuity definition] Patient should be monitored *every eight weeks* for visual acuity following achievement of stable visual acuity. Treatment is resumed with injections every eight weeks when *monitoring indicates vision deterioration* due to DME and continued until stable visual acuity is reached again for <u>three</u> consecutive assessments. The interval between two doses should not be shorter than eight weeks.
Administrative Advice *(to be finalised at a later stage)*	*Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services* *Authority applications for continuing treatment in the same eye may be made by telephone on 1899 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *<u>Note</u>* *No increase in the maximum quantity or number of units may be authorised* *<u>Note</u>* *No increase in the maximum number of repeats may be authorised* *<u>Note</u>* *Special Pricing Arrangements apply.*

2.2 The submission sought listing on the basis of (1) superior efficacy and equivalent comparative safety with laser photocoagulation; (2) superiority with respect to mean difference in change in best corrected visual acuity (BCVA) and equivalent safety with ranibizumab, with cost utility analyses (CUAs) presented for both comparisons; and (3) the assumption that aflibercept would be at least as efficacious and safe as bevacizumab, which informs a cost minimisation analysis (CMA).

2.3 The effective price [redacted] is calculated by weighting aflibercept vial prices derived from the CMA with bevacizumab [redacted] and two CUAs comparing aflibercept against ranibizumab and laser photocoagulation [redacted].

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

3 Background

3.1 TGA status at time of PBAC consideration: Not registered. This is the first consideration of aflibercept for the treatment of diabetic macular oedema by the PBAC. The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, a positive TGA Delegate's summary was available.

3.2 Aflibercept is currently PBS listed for the treatment of subfoveal choroidal neovascularisation due to age-related macular degeneration (AMD); recommended on a cost-minimisation basis against ranibizumab (aflibercept 2mg ≡ ranibizumab 0.5mg) (March 2012).

3.3 At the July 2013 and March 2014 meetings, the PBAC considered aflibercept for the treatment of central retinal vein occlusion (CRVO). In both meetings, the PBAC rejected the submissions on the basis of unacceptably high and likely underestimated cost-effectiveness of aflibercept compared with placebo/best supportive care, and on the basis of inadequate comparative data against bevacizumab.

4 Clinical place for the proposed therapy

4.1 DME is a complication of diabetic retinopathy. It is diagnosed by ophthalmic examination, fluorescein angiography and fundus photography. When DME affects the centre of the macula, it can lead to loss of visual acuity, and if left untreated, to blindness. The natural progression of DME leads to a significant loss (≥10 letters) within two years in 50% of individuals.

4.2 It is proposed that aflibercept will be an alternative to ranibizumab as well as laser photocoagulation for the treatment of visual impairment due to DME. Off label bevacizumab, administered via intravitreal injection would also be replaced in practice.

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

5 Comparator

5.1 The submission nominated laser photocoagulation as the primary comparator, with ranibizumab included as a secondary comparator. The PBAC has recommended that ranibizumab should be listed for the treatment of visual impairment due to diabetic macular oedema (DME) in July 2014. Assuming the listing progresses, the most relevant comparison is between aflibercept and ranibizumab. The Pre-Sub-Committee Response (PSCR) agreed that ranibizumab would be the appropriate

main comparator if it becomes PBS listed however, maintained that laser photocoagulation is the current appropriate primary comparator. The ESC noted that laser would be a common reference for comparisons with ranibizumab and bevacizumab.

5.2 In assessing ranibizumab for DME, the PBAC considered that bevacizumab was also a relevant comparator because it is widely used for the treatment of DME (ranibizumab PSD, March 2013). The sponsor did not accept bevacizumab as a clinical comparator for aflibercept in DME, but a hypothetical economic comparison was presented in the submission. The ESC noted that no formal clinical claim was made to support the CMA.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician addressed the issues raised by ESC regarding the differences in patient/trial characteristics across pivotal trials (VIVID, VISTA, RESTORE and REVEAL), dosing regimens and differences in loading dose. The treat-and-extend approach beyond one year in aflibercept is similar to the PRN dosing in ranibizumab. The clinician further advised that, in clinical practice, the loading dose for aflibercept is likely to be three or less injections in the first year.

6.2 The PBAC sought clarification on the overall treatment duration with aflibercept, assessment of response during the course of treatment and if ceiling (plateau) effect was observed in the trials.

6.3 The PBAC considered that the hearing was informative as it provided clinical perspective on treating this condition.

Consumer comments

6.4 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with aflibercept, including the following:

- fewer side effects compared to laser photocoagulation;
- affordability compared to bevacizumab, noting DME is a bilateral condition;
- 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

6.5 The clinical evidence presented in the submission is based on two comparisons:
(1) Direct head to head comparison of the efficacy and safety of aflibercept versus laser photocoagulation based on two phase 3 trials, VIVID (n=406) and VISTA (n=466);

(2) Indirect comparison of the efficacy and safety of aflibercept versus ranibizumab using laser photocoagulation as the common reference using two phase 3 ranibizumab trials, RESTORE (n=345) and REVEAL (n=396) in addition to the aflibercept trials. The PBAC had also considered the ranibizumab phase 3 DRCR.net trial as well as clinical outcomes from the use of ranibizumab + laser treatment (ranibizumab DME PSDs, March 2013, November 2013). This additional evidence was included in the consideration of effectiveness and safety during the evaluation.

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

Trials and associated reports presented in the submission and additional evidence (DRCR.net trial) identified during the evaluation

Trial ID	Protocol title/ Publication title	Publication citation
Aflibercept trials		
DA VINCI (VGFT-OD-0706)	A Double-Masked, Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema (DME)	2011
	Do DV, Schmidt-Erfurth U, Gonzalez VH, Gordon CM, Tolentino M, Berliner AJ, Vitti R, Rückert R, Sandbrink R, Stein D, Yang K, Beckmann K, Heier JS. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema.	Ophthalmology. 2011; 118(9): 1819-1826
	Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, Berliner AJ, Gao B, Zeitz O, Ruckert R, Schmelter T, Sandbrink R, Heier JS; da Vinci Study Group. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema.	Ophthalmology. 2012; 119(8): 1658-1665
VIVID (PH-37284)	A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema	2013
	Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, Midena E, Kaiser PK, Terasaki H, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Brown DM Intravitreal Aflibercept for Diabetic Macular Edema	Ophthalmology. 2014. pii: S0161-6420(14)00426-6
VISTA (VGFT-OD-1009)	A Double-Masked, Randomized, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema	2013
	Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, Midena E, Kaiser PK, Terasaki H, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Brown DM Intravitreal Aflibercept for Diabetic Macular Edema	Ophthalmology. 2014. pii: S0161-6420(14)00426-6
Ranibizumab trials		
RESTORE	Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, Gerstner O, Bouazza AS, Shen H, Osborne A, Mitchell P; RESTORE Extension Study Group. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study.	Ophthalmology. 2014; 121(5):1045-1053
	Boixadera A, Garcia-Arumi J. 36-month safety and efficacy of ranibizumab in diabetic macular oedema: The RESTORE extension study (final	Diabetologica. 2013; 56:S28-29

	analysis).	
	Lang GE, Berta A, Eldem BM, Simader C, Sharp D, Holz FG, Sutter F, Gerstner O, Mitchell P; RESTORE Extension Study Group. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study.	Ophthalmology. 2013; 120(1):2004-2012
	Mitchell P, Bressler N, Tolley K, Gallagher M, Petrillo J, Ferreira A, Wood R, Bandello F; RESTORE Study Group. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial.	JAMA Ophthalmology. 2013; 131(10): 1339-1347
	Lang GE. Long-term safety and efficacy of ranibizumab 0.5mg in patients with diabetic macular oedema of the RESTORE extension study.	Diabetologica. 2012; 55(Supp1): S85
	Knudsen MS, Thomas S, Gallagher M, Mitchell P. Assessment of utility loss from diabetic macular edema based on RESTORE trial.	Value in Health. 2011; 14(7): A507
	Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, Sutter F, Simader C, Burian G, Gerstner O, Weichselberger A. The RESTORE Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema.	Ophthalmology. 2011; 118.4:615-625
	Massin P. Efficacy and safety of ranibizumab monotherapy or adjunctive with laser versus laser therapy in patients with diabetic macular oedema: 12-month results of the RESTORE study.	Diabetologica. 2010; 53(Supp1): S472
	Mitchell O. Restore trial of ranibizumab for diabetic macular oedema: 1-year findings.	Clinical and Experimental Ophthalmology. 2010; 38(Suppl2): 12
REVEAL	Ohji M, Ishibashi T (Snr), REVEAL study group. Efficacy And Safety Of Ranibizumab 0.5 Mg As Monotherapy Or Adjunctive To Laser Versus Laser Monotherapy In Asian Patients With Visual Impairment Due To Diabetic Macular Edema: 12-month Results Of The REVEAL Study	Investigative Ophthalmology and Visual Science. 2012;53: E-Abstract 4664
READ-2	Channa R, Sophie R, Khwaja AA, Do DV, Hafiz G, Nguyen QD, Campochiaro PA, READ-2 Study Group. Factors affecting visual outcomes in patients with diabetic macular edema treated with ranibizumab.	Eye. 2014: 28(3): 269-278
	Do DV, Nguyen QD, Khwaja AA, Channa R, Sepah YJ, Sophie R, Hafiz G, Campochiaro PA, READ-2 Study Group. Ranibizumab for Edema of the Macula in Diabetes Study.	JAMA Ophthalmology. 2013; 131(2): 139-145
	Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, Boyer D, Heier JS, Abraham P, Thach AB, Lit ES, Foster BS, Kruger E, Dugel P, Chang T, Das A, Ciulla TA, Pollack JS, Lim JI, Eliott D, Campochiaro PA; READ-2 Study Group. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study.	Ophthalmology. 2010; 117(11): 2146-2151
	Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, Abraham P, Campochiaro PA; READ-2 Study Group. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study.	Ophthalmology. 2009; 116(11): 2175-2181

	Nguyen QD, Heier JS, Shah SM, Lim JI, Campochiaro PA, The READ 2 Investigators. Six-Month Results of the READ 2 Study: Ranibizumab for Edema of the Macula in Diabetes, a Phase 2 Clinical Trial	American Journal of Ophthalmology. 2008: 180
LUCIDATE	Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, Bunce CV, Patel PJ, Egan CA, Bainbridge JW, Hykin PG. A Randomized Trial to Assess Functional and Structural Effects of Ranibizumab versus Laser in Diabetic Macular Edema (the LUCIDATE Study).	American Journal of Ophthalmology. 2014; 157(5): 960-970
LIME	Goodart RA, Faber DW, Mehr DS, Murphy H, Gleed J. Lucentis in the Treatment of Macular Edema (LIME): A Phase II Study Evaluating the Safety and Efficacy of Ranibizumab versus Focal Laser Treatment in Patients With Diabetic Macular Edema	Investigative Ophthalmology and Visual Science. 2007; 48: E-Abstract 1431
DRCR.net* (NCT0044503)	Elman MJ, Aiello LP, Beck RW, Bressler NM, Breslller SB, Edwards AR, Ferris III FL, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema Elman MJ, Bressler NM, Qin H, Beck RW, Ferris III FL, Friedman SM, Glassman AR, Scott IU, Stockdale CR, Sun JK. Expanded 2-Year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema	Ophthalmology.2010; 117:1064-1077 Ophthalmology. 2011; 118:609-614

* DRCR.net was included in the clinical evaluation following a review of the literature search conducted by the submission.
Source: Table B.2.2, pp13-16, Section B of the submission

6.7 The key features of the randomised trials are summarised in the table below. The clinical claims made by the submission are based on the aflibercept every 8 weeks (2Q8) treatment arms of VIVID and VISTA. Aflibercept was administered as monthly intravitreal injections for five visits, followed by 2Q8 treatment on an ongoing basis.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation
Aflibercept vs laser photocoagulation						
VIVID	406	R, DM, AC, MC, Phase 3; 52 week results	Low	Vision impairment (BCVA: 73-24) due to DME	Change from baseline in BCVA in ETDRS letter score at week 52	Transition probabilities (year 1), adverse events
VISTA	466	R, DM, AC, Phase 3; 52 week results	Low			
Meta analysis	*872*	VIVID and VISTA pooled analysis of aflibercept 2Q8 and laser				
Ranibizumab vs laser photocoagulation						
RESTORE	*343*	R, DM, MC, Phase 3; 12 month results	Low	Vision impairment (BCVA: 78-39) due to DME	Change in BCVA letter score from baseline to month 1 through month 12	RR for gain/loss ≥10 & ≥15 letters are used to calibrate aflibercept transition probabilities (year 1); adverse events (RESTORE)
REVEAL	396	R, DM, MC, Phase 3; 12 month results	Unclear; insufficient information			
Meta analysis	*739*	RESTORE and REVEAL pooled analysis of ranibizumab monotherapy and laser				

Abbreviations: AC = active control; BCVA = best corrected visual acuity; DM = double masked; MC = multicentre; R = randomised; RR = relative risk. Source: compiled during the evaluation

Comparative effectiveness

6.8 Key results for the outcome of mean change in baseline BCVA in ETDRS letter score at 12 months are presented in the table below.

Mean change in baseline BCVA in ETDRS letter score at 12 months

		VIVID		VISTA	
		2Q8 (n=135)	**Laser (n=132)**	**2Q8 (n=151)**	**Laser (n=154)**
Baseline	Mean; SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 52		[redacted]	[redacted]	[redacted]	[redacted]
Δ b/line to 52/52		[redacted]	[redacted]	[redacted]	[redacted]
AFB vs laser	MD; 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Meta-analysis: aflibercept vs laser (MD, 95% CI)		Aflibercept 2Q8 vs laser: [redacted]			
N		**RESTORE**		**REVEAL**	
		RBZ+SL (n=115)	**SI+L (n=110)**	**RBZ+SL (n=133)**	**SI+L (n=128)**
Baseline	Mean; SD	[redacted]	[redacted]	[redacted]	[redacted]
Yr 1		[redacted]	[redacted]	[redacted]	[redacted]
Δ b/line to Yr 1		[redacted]	[redacted]	[redacted]	[redacted]
RBZ vs laser	MD; 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Meta-analysis: ranibizumab vs laser (MD, 95% CI)		Ranibizumab vs laser: [redacted]			
Indirect comparison		Aflibercept 2Q8 vs ranibizumab: [redacted]			

Statistically significant differences for the comparison versus laser are highlighted in **bold**

Abbreviations: AFB = aflibercept; DL = deferred laser; MD = mean difference; ne = number of eyes; NR = not reported; PL = prompt laser; RBZ = ranibizumab; SI = sham injection; SL = sham laser; Source: Table B.6.1, p71, Section B of the submission

6.9 In the meta-analysis, there was a statistically significant difference in favour of aflibercept 2Q8 [redacted] for mean change in baseline BCVA in ETDRS letter score at 12 months for the comparison with laser photocoagulation.

6.10 Key results for the secondary outcomes from the randomised trials are presented in the table below.

Secondary outcomes from the randomised trials

		Patients who gained ≥10 letters			Patients who gained ≥15 letters			Patients who lost ≥10 letters			Patients who lost ≥15 letters		
		n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)
Aflibercept trials													
VIVID	2Q8												
	Laser												
VISTA	2Q8												
	Laser												
Meta analysis*	AFB 2Q8 vs laser (VISTA & VIVID)												
Ranibizumab trials													
RESTORE	RBZ+SL												
	RBZ+Laser												
	SI+Laser												
REVEAL	RBZ+SL												
	RBZ+Laser												
	SI+Laser												
DRCR.net'	RBZ+DL												
(n eyes/N eyes)	RBZ+PL												
	PL												

		Patients who gained ≥10 letters			Patients who gained ≥15 letters			Patients who lost ≥10 letters			Patients who lost ≥15 letters		
		n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)	n/N (%)	RR (95% CI)	RD% (95% CI)
		[redacted]			[redacted]			[redacted]			[redacted]		
Meta analysis*	RBZ vs laser (RESTORE, REVEAL)												
	RBZ vs laser (RESTORE, REVEAL, DRCR.net)												
	RBZ + laser vs laser (RESTORE, REVEAL, DRCR.net)												
Indirect comparison*	AFB 2Q8 (VIVID, VISTA) vs RBZ (RESTORE, REVEAL)												
	AFB 2Q8 (VIVID, VISTA) vs RBZ (RESTORE, REVEAL, DRCR.net)												
	AFB 2Q8 (VIVID, VISTA) vs RBZ+ laser												

*Additional analyses were conducted during the evaluation using Stats Direct Version 2.7.9. RDs for the indirect comparisons were recalculated during the evaluation given that SE used by the submission did not appropriately account for the upper and lower confidence intervals (refer to Section B.5). Abbreviations: AFB = aflibercept DL = deferred laser; PL = prompt laser; RBZ = ranibizumab; SI = sham injection; SL = sham laser. Source: Table B.6.5, pp84-85, Section B of the submission and the relevant publications

6.11 In the indirect comparison, a statistically significant difference (mean difference: 4.81, 95% CI: 2.51, 7.11) in favour of aflibercept 2Q8 was observed from the comparison with ranibizumab monotherapy. Similar differences were observed with the addition of results from DRCR.net and the comparison with ranibizumab + laser. The submission claimed that this statistically significant difference supports the claim of superiority of aflibercept in the change in BCVA in ETDRS letter score compared to ranibizumab (p82, Section B).

6.12 The ESC questioned whether the trials used as the basis of the indirect comparison are sufficiently comparable to use for determining comparative effectiveness. There are differences in the trial populations in terms of weight, duration of diabetes, race, prior exposure to treatment with anti-VEGF products, and baseline visual acuity. The method for determining change in BCVA was not the same. The dosing regimen for aflibercept is also different across the two trials and the TGA has yet to finalise the recommended dose.

6.13 The ESC noted the following points:

- Although the indirect comparison of aflibercept 2Q8 and ranibizumab monotherapy for mean difference in BCVA from baseline to 12 months in ETDRS letter score resulted in a statistically significant letter gain of 4.81 in favour of aflibercept, the PBAC has previously considered that a 10-letter gain is required to achieve a clinically significant improvement in vision related quality of life (ranibizumab DME PSD, November 2013). The gain in letters by aflibercept compared to ranibizumab is less than half of that previously accepted to be clinically significant.
- Although point estimates from the indirect comparisons of secondary outcomes (i.e. such as patients who gained/lost at least 10 and 15 ETDRS letters in BCVA) suggest an advantage for aflibercept when compared to ranibizumab, consistent statistically significant differences in favour of aflibercept were not observed across the analyses.

Comparative harms

6.14 Overall, there were low incidences of serious ocular adverse events (AE) in the randomised trials. One death in the VIVID trial due to hypertensive heart disease was considered to be related to aflibercept. No deaths from the ranibizumab trials (RESTORE, REVEAL) were considered related to the study drug.

6.15 The non-ocular treatment emergent adverse events of anaemia (VIVID: 2.2% vs 0.8%; VISTA: 6.6% vs 3.9%) and neoplasms (benign, malignant and unspecified: VIVID: 4.4% vs 2.3%; VISTA: 5.3% vs 2.6%) appeared to be more common in aflibercept treated patients compared to laser, although no statistically significant differences were observed. As for cardiovascular events, there were no significant trends observed in non-fatal myocardial infarction, non-fatal stroke or vascular death as per the Antiplatelet Trialists' Collaboration (APTC) Criteria (refer to table below).

Cardiovascular events according to the Antiplatelet Trialists' Collaboration (APTC)

	VIVID		**VISTA**		***DRCR.net***	
	2Q8 (n=135)	**Laser (n=133)**	**2Q8 (n=152)**	**Laser (n=154)**	***Ranibizumab (n=375)^***	***Laser (n=130)^***
Non fatal MI	0	1 (0.8)	3 (2.0)	4 (2.6)	***1 (0.3)***	*3 (2.3)*

Non fatal stroke	2 (1.5)	0	3 (2.0)	2 (1.3)	***3 (0.8)***	*5 (3.8)*
Vascular death	2 (1.5)	1 (0.8)	0	1 (0.6)	*7 (1.9)*	*4 (3.1)*
Any APTC event	4 (3.0)	2 (1.5)	6 (3.9)	6 (3.9)	***11 (2.9)***	*10 (7.7)*

Note: Statistically significant differences for the comparison versus laser are highlighted in **bold**
^ n=number of study participants, Study participants with 2 study eyes are assigned to the non-sham group. Multiple events within a study participant are only counted once per event. Source: Table 55, p152, VISTA CSR; Table 64, p147, VIVID CSR; Table 17, Elman 2010.

6.16 No notable differences were observed between aflibercept and laser, ranibizumab and laser or for the indirect comparison for the key overall AE outcomes (fatal AEs, serious AEs, serious ocular AEs, ocular AEs).

Benefits/harms

6.17 A summary of the comparative benefits and harms for the indirect comparison of aflibercept versus ranibizumab as well as the direct comparison versus laser photocoagulation are presented in the table below.

Summary of comparative benefits and harms for the aflibercept, ranibizumab and laser photocoagulation

Trial	AFB 2Q8	Laser	RBZ 0.5mg	RR (95% CI)	Event rate/100 patients*			RD% (95% CI)
					AFB	Laser	RBZ	
Benefits								
Mean change in baseline BCVA in ETDRS letter score at 12 months								
	AFB 2Q8 or RBZ 0.5mg vs laser photocoagulation			**Indirect comparison: AFB 2Q8 vs RBZ 0.5mg; MD: (95%CI)**				
	n	**MD (95% CI)**						
VIVID, VISTA: meta analysis	572	10.01 (8.32, 11.69)		4.81 (2.51, 7.11)				
RESTORE, REVEAL meta-analysis	486	5.19 (3.63, 6.75)						
Harms								
Trial	**AFB 2Q8**	**Laser**	**RBZ 0.5mg**	**RR (95% CI)**	**Event rate/100 patients***			**RD% (95% CI)**
					AFB	**Laser**	**RBZ**	
Serious adverse events								
VIVID & VISTA: meta-analysis	72/287	78/287	-	0.95 (0.62, 1.47)	25.1	27.2	-	-1.0 (-13.0, 10.0)
REVEAL	-	19/128	21/133	1.06 (0.60, 1.88)	-	14.8	15.8	0.9 (-7.8, 9.7)
Indirect comparison: aflibercept vs ranibizumab				0.90 (0.44, 1.83)	-			-1.9 (-16.4, 12.6)
Ocular adverse events								
VIVID & VISTA: meta-analysis	202/287	204/287	-	0.99 (0.89, 1.10)	70.4	71.1	-	-1.0 (-8.0, 7.0)
RESTORE	-	43/110	49/115	1.09 (0.80, 1.49	-	39.1	42.6	3.5 (-9.3, 16.4)
Indirect comparison: aflibercept vs ranibizumab				0.91 (0.65, 1.26)	-			-4.5 (-19.4, 10.4)

* Duration of follow-up: 52 weeks: VIVID, VISTA; 12 months: RESTORE, REVEAL. Abbreviations: AFB = aflibercept; BCVA = best corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; MD = mean difference; RBZ = ranibizumab; RD = risk difference; RR = risk ratio; Source: Compiled during the evaluation

6.18 On the basis of direct evidence presented by the submission, for patients treated with aflibercept there would be:

- approximately a 10.01 letter gain in BCVA for aflibercept when compared to laser photocoagulation over a 12-month duration of follow-up

On the basis of the indirect comparison of aflibercept with ranibizumab, there would

be:

- approximately a 4.81 letter gain in BCVA for aflibercept when compared to ranibizumab over a 12-month duration of follow-up. However, this difference may be an artefact of the difference in trial populations and does not represent a clinically significant improvement in vision-related quality of life.

6.19 On the basis of the indirect comparison presented, the frequency of adverse effects over 12 months appears to be similar for patients treated with either aflibercept or ranibizumab.

Clinical claim

6.20 The submission described aflibercept as superior in terms of comparative effectiveness over laser photocoagulation. This claim was considered to be adequately supported for the one year primary endpoint analyses, although the following questions were noted:
(1) whether the long term effectiveness of aflibercept for the treatment of DME will be sustained given that two to three year efficacy outcomes have yet to be reported;
(2) effects upon health related quality of life: EQ-5D outcomes from VIVID indicated minimal change from baseline to week 52 in the treatment groups and the VISTA CSR did not report EQ-5D results. .

6.21 The submission described aflibercept as superior in terms of efficacy with respect to mean difference in change in BCVA letter score over ranibizumab. The evaluation noted that although a statistically significant letter gain of 4.81 (95% CI: 2.51, 7.11) in favour of aflibercept was estimated for the indirect comparison, the PBAC has previously considered that a 10-letter gain is required to achieve a clinically significant improvement in vision related quality of life (ranibizumab DME PSD, November 2013). The ESC agreed with the evaluation and considered that, while this difference is statistically significant, the formal indirect comparison of other outcomes (i.e. such as patients who gained/lost at least 10 and 15 ETDRS letters in BCVA) does not show consistent statistically significant differences in favour of aflibercept.

6.22 The submission described aflibercept as equivalent in terms of safety over laser photocoagulation and ranibizumab. Although the trial evidence is supportive of an equivalent safety claim for aflibercept, results are limited to a 1 year analysis.

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

Economic analysis

6.23 Two economic evaluations were presented by the submission:
(1) CUA based on the comparisons of aflibercept vs laser photocoagulation and aflibercept vs ranibizumab (aflibercept vial price = [redacted]);
(2) CMA based on the comparison of aflibercept vs bevacizumab (aflibercept vial price = [redacted]).

6.24 <u>CUA: aflibercept vs laser photocoagulation and aflibercept vs ranibizumab:</u> The submission presented a nine state (8 VA health states plus death) Markov state transition model. Treatment was modelled through the application of relevant utilities

associated with the better seeing eye (BSE) or worse seeing eye (WSE) status of the treated eye. The overall ICER was calculated via a [redacted] distribution:

1. Unilaterally in the WSE [redacted]: The PBAC has previously considered that a discernible effect on overall VA would occur in patients for whom the treated eye was the BSE after 12 months follow up, and where the treated eye was originally the WSE (ranibizumab DME November 2013 PSD, p6). This scenario was not considered in the economic model. It was assumed that, following treatment, the WSE status of the treated eye does not change for the entire duration of the model.
2. Bilateral [redacted]: cumulative QALYs from treatment in the BSE and WSE as well as associated costs inform the estimated ICER. The assumption that treatment will occur in a WSE [redacted]/bilateral [redacted] distribution on the basis of VISTA was inadequately justified, given the significant differences in the extent of fellow eye treatment across the aflibercept trials. Additionally, a significantly lower proportion of patients with bilateral disease (12%) have been observed in population based studies (Petrella 2012). Overall, it is likely that the extent of bilateral treatment has been overestimated by the submission.

6.25 The submission described the economic model as a 'one eye model'. However, the evaluation of the model found that both the study eye and non-study eye were modelled in a unilateral ([redacted] treated eye/fellow eye) and bilateral ([redacted]: treated eye/treated eye) scenario. This two eye framework for both unilateral and bilateral settings, leads to a situation where each treated eye VA health states each have 64 associated fellow eye transitions. In its entirety, the model uses [redacted] readjusted transition probabilities for unilateral and bilateral treatment in the efficacy phase. It is unclear why the submission utilised such an extensive approach, when the utility inputs were based on the VA in the BSE or WSE and not on a combination of VA in both eyes. Conceptually, there is also structural disconnect between the single eye BSE/WSE utilities and transitions which are informed by 4 or 8 eyes. Overall, the level of specificity in the model is unlikely to contribute to the reliability of the estimated ICER. The PSCR stated that the model in the submission retains features of a two-eye model, but results are generated only for the study eye using 64 transition probabilities with many of the transition probabilities in specific cycles being zero.

Summary of model structure and rationale

Component	Summary
Time horizon	15 years in the model base case versus 1 year in the trials
Outcomes	Cost/QALY
Methods used to generate results	Markov state transition model incorporating 3 distinct phases: (1) Efficacy phase: Year 1 (2) Maintenance Phase: Year 2 & 3 – VA is assumed to remain stable (3) Rest of life phase: Year 4 to 15 – long term decline in VA with age as informed by ETDRS
Health states	8 VA health states and death
Cycle length	Year 1-2: 4 weeks; Year 2-15: 1 year
Transition probabilities (efficacy phase – year 1)	Aflibercept, Laser: Derived from an integrated analysis of VISTA and VIVID. Although methods used by the submission were appropriate, the number of VA health states resulted in limited patient samples populating the VA subgroups, especially in the lower VA health states Ranibizumab: The deterministic calibration model used to derive ranibizumab transition probabilities was informed by the RR of gain/loss of 10/15 letters from the pooled analysis of RESTORE and REVEAL. Given that no statistically significant relative risks were observed for the secondary outcomes in the indirect comparison of aflibercept 2Q8 and ranibizumab

Component	Summary
	monotherapy, it is questionable as to whether the calibrated transition probabilities are a reliable means of deriving any potential differences in VA.

Abbreviations: ETDRS = early treatment diabetic retinopathy study; VA = visual acuity.
Source: compiled during the evaluation

6.26 Key drivers of the model are summarised in the table below.

Key drivers of the model

Description	Method/Value	Impact	
		Aflibercept vs laser	Aflibercept vs ranibizumab
Utilities	BSE: Czosky-Murray 2009 WSE: 30% of the difference of that in the BSE	High, favours aflibercept	
Time horizon	15 years, assumed from 1 year trial duration	High, favours aflibercept	
Injection frequencies	Year 1: 9.8; Year 2: 4.9	High, favours aflibercept	
Duration of treatment	Limited to 2 years	High, favours aflibercept	
Adverse events	Costs and disutilities: cataract, vitreous haemorrhage and ATE	Low	High, favours aflibercept

Abbreviations: ATE = arterial thromboembolic events; BSE = best seeing eye; WSE = worse seeing eye
Source: compiled during the evaluation

6.27 Utilities for the BSE were based on a time trade off study (Czosky-Murray 2009), where vision states were simulated in a general patient cohort. There are significant concerns as to the appropriateness of the simulated vision impairment scenarios used in Czosky-Murray 2009, given the likelihood that these methods significantly overstate health related quality of life differences based on changes to VA.

6.28 The submission's approach to the derivation of WSE utilities involved an adjustment to account for [redacted] of the difference of that in the BSE as utilised in prior NICE evaluations. The ESC considered that this adjustment was arbitrary and may not adequately represent health related quality of life associated with VA changes in the WSE. There is the potential that differences in WSE utilities may be more pronounced in cases where visual acuity of the BSE is lower. Therefore, to simply apply a proportional reduction to BSE utility differences is unlikely to adequately inform WSE utilities.

6.29 The submission did not discuss the use of trial based utilities in the economic model. In VIVID and VISTA, the EQ-5D was administered at baseline, Week 24 and Week 52. Although minimal changes in the EQ-5D from baseline to Week 52 in treatment groups were observed in VIVID, point estimates of treated eye utilities according to the VA health states presented in the economic model potentially indicate some differences across VA health states. Although treated eye utilities are not applicable for an economic evaluation based on a 'one eye BSE/WSE model', given the above concerns associated with the methods used in Czosky-Murray 2009 and the arbitrary approach applied in the derivation of utilities for the WSE, it would have been more appropriate if the submission had provided greater regard to the use of trial based utilities for the BSE and WSE from VISTA and VIVID. The ESC considered that the utilities in Czosky-Murray were likely to be overestimated and considered that the trial based EQ-5D utilities may be more appropriate.

6.30 The ESC noted that the statistical analyses conducted by the evaluation indicated there were no significant differences for the direct comparison of aflibercept vs. laser and the indirect comparison of aflibercept and ranibizumab in regard to the adverse events of cataract, vitreous haemorrhage, ocular hypertension and arterial thromboembolic events. The ESC considered that there was insufficient justification for the consideration of these adverse events, which is further compounded by the lack of reliable sources informing the disutility values used in the economic evaluation. In regard to the comparison of aflibercept and ranibizumab, the ESC noted that the economic model was highly sensitive to the removal of costs and utilities associated with adverse events, resulting in a [redacted] increase over the base case ICER.

6.31 The ESC noted that the submission used Christ et al (2008) study in the model to estimate the direct and indirect effects of self-reported visual impairment on mortality, similar to the March 2014 and concurrent submission for CRVO. The ESC considered that the addition of indirect effects (via disability and self-rated health) to direct effects on mortality resulted in a stronger association between visual impairment and mortality, with differences most prominent in the severe visual impairment category. Furthermore, background probabilities of death per year adjusted for diabetes are multiplied by the RR of mortalities informed by Christ 2008 for the VA7 and VA8 health states. The application of hazard ratios across the VA7 and VA8 health states irrespective of treatment in BSE or WSE does not reflect the prospect that the BSE is most likely to correlate with a patient's risk of mortality.

Hazard ratios of the direct and indirect effects of visual impairment on mortality

	Hazard ratio (95% CI)		
	Direct effects on mortality	Indirect^ & direct effects on mortality	Indirect & direct effects on mortality: subset analysis
	N=135,581		N=40,211
Some visual impairment‡	1.13 (1.07, 1.20)	1.23 (1.16, 1.31)	1.16 (1.05, 1.28)
Severe visual impairment‡	1.28 (1.07, 1.53)	1.54 (1.28, 1.86)	1.48 (1.15, 1.89)

‡ Severe visual impairment = blind in both eyes; Some visual impairment: visual impairment in both eyes, blind in one eye, visual impaired in the other eye, blind or visually impaired in one eye only, with the other eye having good vision or not mentioned. ^ Indirect effects on mortality included those through disability and self-rated health. Source: Table 1, Table 2, p8, Christ 2008

Application of hazard ratios in the economic evaluation

VA health states:	HR applied in the economic evaluation
Treated eye: VA7 or VA8 Fellow eye: VA1, VA2, VA3, VA4, VA5 or VA6	[redacted]
Treated eye: VA1, VA2, VA3, VA4, VA5 or VA6 Fellow eye: VA7 or VA8	[redacted]
Treated eye: VA7 or VA8 Fellow eye: VA7 or VA8	[redacted]

Source: Constructed during the evaluation

6.32 The ESC noted the issues with the model and that the structure of the model could not be verified. Overall, the ESC considered that the model was unlikely to be reliable.

6.33 The table below provides the results of the economic evaluation.

Results of the economic evaluation

Component	AFB	RBZ	Laser	Increment	
				AFB vs RBZ	AFB vs laser
WSE (35%)					
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost/QALY				[redacted]	[redacted]
BSE*					
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost/QALY				[redacted]	[redacted]
Bilateral (65%)					
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost/QALY				[redacted]	[redacted]
Final weighted analysis					
Cost	NC			[redacted]	[redacted]
QALY				[redacted]	[redacted]
Overall incremental cost/QALY				[redacted]	[redacted]

* The BSE analysis is incorporated into the estimates for bilateral treatment, which essentially is the culmination of incremental costs and outcomes from the BSE & WSE. The submission assumes that treatment will only occur in the WSE and bilaterally in a [redacted] distribution.

Abbreviations: AFB = aflibercept; BSE = best seeing eye; RBZ = ranibizumab; WSE = worse seeing eye

Source: Table D.5.12, Table D.5.13, p43-44, Section D-CEA of the submission

6.34 Aflibercept vs laser: The ESC advised that it is most likely that QALY gains [redacted] have been substantiallyoverestimated given the application of utilities from Czosky-Murray 2009. Additionally, the assumption of a [redacted] maximum duration of treatment may underestimate incremental costs associated with aflibercept. Whilst these are the main factors contributing to the ICER being underestimated, this is in the context of structural issues that impact upon the reliability of the model:
(1) divergence from a 'one eye approach' through the readjustment of transition probabilities derived from the study eye and non-study eye across unilateral and bilateral treatment scenarios; and
(2) reliability of transition probabilities given the 8 VA health states used in the model.

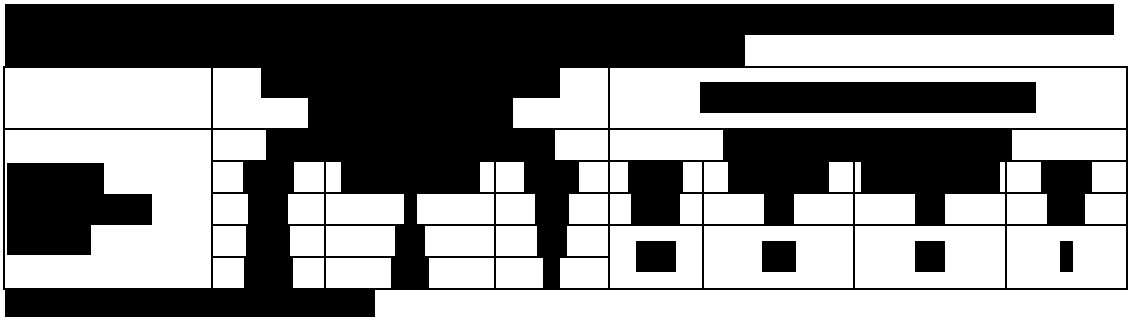
6.35 Aflibercept vs ranibizumab: A calibration model was used to derive ranibizumab transition probabilities for the efficacy phase of the model (year 1). This involved the adjustment of laser transition probabilities from VIVID and VISTA for secondary outcomes (relative risk of gain/loss of 10/15 letters) from a pooled analysis of RESTORE and REVEAL. Given that no statistically significant relative risks were observed for the secondary outcomes in the indirect comparison of aflibercept 2Q8 and ranibizumab monotherapy, the ESC questioned whether the calibrated transition probabilities are a reliable means of deriving any potential differences in VA. The ESC also questioned whether the estimated ICER is meaningful, given that the modelled treatment effect of ranibizumab was primarily informed by non-statistically significant differences in the clinical evidence.

6.36 Sensitivity analyses indicated the model was most sensitive to time horizon, utility value data source, assumed duration of treatment and discount rate. It was also observed that, for the comparison of aflibercept and ranibizumab, the model was sensitive to the exclusion of adverse events [redacted]) and the adjustment

of injection frequencies for aflibercept to reflect the ongoing treatment regimen used in the phase 3 trials (Year 1: [redacted]; Year 2: [redacted]; ICER = [redacted]).

6.37 Overall, the ESC considered that a cost-minimisation analysis between aflibercept and ranibizumab would be a more appropriate approach and the equi-effective doses would need to be established. The ESC also noted the differences in the average dose frequency (and duration) between the two drugs, which will be determined once final TGA dosing recommendations are available.

Committee-in-Confidence



End-Committee-in-Confidence

6.38 CMA: aflibercept vs bevacizumab: The equi-effective doses were estimated as aflibercept [redacted] injections and bevacizumab [redacted] injections over the first year of therapy. No formal clinical claim was made to support the CMA. The inclusion of adverse event costs in the CMA was considered to be questionable given the non-systematic approach used by the submission 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]
Total drug and administration costs per patient: Year 1	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]
Total costs per patient: Year 1	[redacted]	[redacted]

Source: Table D.2.4, p15, Section D-CMA of the submission

6.39 The submission requested a price premium for aflibercept [redacted] over bevacizumab 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 [redacted] for the comparison with bevacizumab.

6.40 On the basis of the aflibercept vial prices used in the economic evaluations, the overall effective price [redacted] was informed by a [redacted] distribution across ranibizumab/bevacizumab/laser as comparators.

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

Drug cost/patient/year:

6.41 The drug cost/patient/year was estimated to be [redacted] in Year 1; [redacted] in Year 2; [redacted] in Year 3; [redacted] in Year 4 and [redacted] in Year 5.

6.42 The drug cost/patient/year estimate was based on an average number of aflibercept injections per treated eye (Year 1: [redacted], Year 2: [redacted], Year 3: [redacted], Year 4 & 5: [redacted]), which were then adjusted for the expected extent of bilateral treatment [redacted]. As to whether these trial based treatment frequencies (Year 1 and Year 2) will eventuate in practice is dependent upon the following factors.

1) Reduction in out of pocket costs with the proposed listing may result in increased accessibility to treatment and adoption of ongoing treatment practices ([redacted] injections in year 1 and [redacted] injections per year thereafter for the treated eye).
2) Ongoing treatment schedules may be impracticable, given the considerable burden this may impose on patients. There is the potential that aflibercept may be administered on a PRN basis in such circumstances.

Estimated PBS usage & financial implications

6.43 This submission was not considered by DUSC.

Estimated financial implications for the PBS

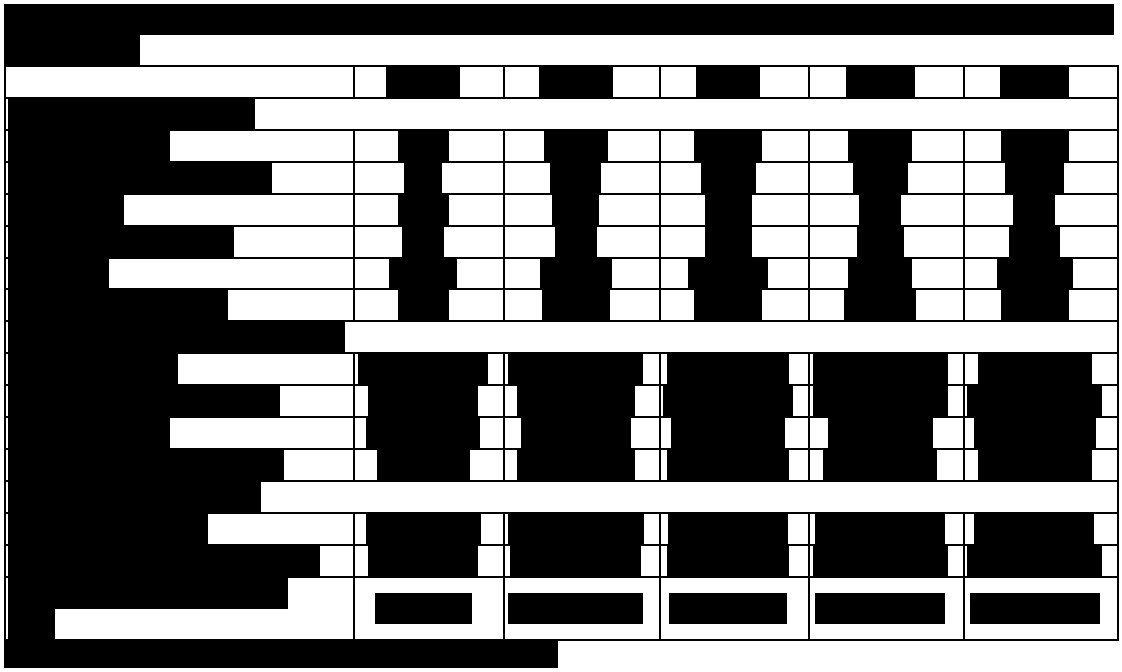
	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept treated DME patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total aflibercept injections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payments ($10.91 per injection)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: During the evaluation the financial estimates were updated to reflect the most recent ABS Australian population projections (ABS 3222.0 Series B, 2013). Source: Table E.2.4, Section E of the submission

The redacted table shows:
Estimated patient numbers: 10,000 – 50,000 in Year 1, increasing to
50,000 – 100,000 per year in Year 5;
Estimated injections: over 200,000 in Year 1, decreasing to over 200,000 in Year 5;
Estimated financial impact: Cost of more than $100 million per year in Year 1, decreasing to a cost of more than $100 million per year in Year 5.

6.44 The reliability of the base case estimates depended on the assumption that [redacted] of the population with clinically significant macular oedema (CSME) has visual impairment. This assumption resulted in [redacted] of patients with diabetes having visual impairment due to DME. Considering that smaller proportions of DME patients with VI have been reported (2.93%, Petrella 2012), the ESC considered it probable that the submission's [redacted] assumption is a [redacted] overestimate. Halving the extent of VI in the CMSE population ([redacted]) resulted in a [redacted] decrease in net costs to the PBS over 5 years. Overall, a highly conservative approach has been used by the submission, which is likely to result in net costs to the PBS being significantly overestimated.

Committee-in-Confidence



End-Committee-in-Confidence

6.45 The PBAC noted that the submission did not propose a risk sharing arrangement. Therefore, the Committee recommended that the Department ensure a subsidisation cap be put in place, based on the financial estimates derived using the treatment duration in the trial.

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 visual impairment due to diabetic macular oedema (DME). 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 are aflibercept 2 mg injection : 1.5 mg bevacizumab injection. The PBAC noted the bevacizumab equi-effective dose for this submission is different with the submission for aflibercept for

central retinal vein occlusion (CRVO) also considered on the November 2014 agenda (item 7.1 refers). The PBAC considered that this was due to the different trial data available for bevacizumab for each indication.

7.4 The PBAC further considered that the data provided did not enable any further differentiation across these three alternative VEGF inhibitors by dose frequency or treatment duration for DME.

7.5 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 the recommended criteria for 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, bevacizumab, and laser photocoagulation for the treatment of visual impairment due to DME.

7.7 The PBAC noted that a final TGA decision will be available in early 2015.

7.8 The PBAC noted that the primary comparator nominated by the submission was laser photocoagulation, with ranibizumab as a secondary comparator and bevacizumab as a hypothetical economic comparator. The PBAC agreed with ESC that ranibizumab is the appropriate comparator and maintains that bevacizumab is also a relevant comparator.

7.9 The PBAC accepted the indirect comparison of aflibercept and ranibizumab trials and that the trials are sufficiently exchangeable to use for determining comparative effectiveness. The PBAC considered that, although a statistically significant letter gain of 4.81 (95% CI 2.51, 7.11) in favour of aflibercept 2mg every eight weeks (2Q8) was observed from the indirect comparison, the gain in letters by aflibercept compared to ranibizumab is less than half of that previously accepted to be clinically significant. The PBAC recalled its previous consideration that a 10-letter gain is required to achieve a clinically significant improvement in vision-related quality of life (ranibizumab DME PSD, November 2013). The PBAC also considered that while this difference is statistically significant, the formal indirect comparison of other outcomes (i.e. such as patients who gained/lost at least 10 and 15 ETDRS letters in BCVA) did not show consistent statistically significant differences in favour of aflibercept. Therefore, the PBAC did not accept the submission's claim of superiority with respect to mean difference in change in BCVA with ranibizumab. The PBAC considered that the indirect comparison indicates that aflibercept is non-inferior in terms of efficacy compared to ranibizumab. The PBAC also accepted that aflibercept is non-inferior in terms of safety compared to ranibizumab.

7.10 The PBAC noted that the submission provided no formal clinical comparison to support its cost-minimisation analysis against bevacizumab. The submission identified one randomised trial in DME comparing bevacizumab 1.5 mg and ranibizumab 0.5 mg (Nepomuceno 2013) which could establish equi-effective doses by indirectly comparing injection numbers for aflibercept and bevacizumab via ranibizumab. The PBAC also noted that, although the submission did not provide evidence to support clinical equivalence or superiority, the submission's approach implicitly assumed similar efficacy and safety to bevacizumab based on the claim that aflibercept is superior to ranibizumab. On the totality of the evidence available, it is reasonable to conclude non-inferiority across all three VEGF inhibitors.

7.11 The PBAC noted that the submission presented two economic evaluations, a cost-utility analysis based on the comparisons of aflibercept versus laser photocoagulation and aflibercept versus ranibizumab and a cost-minimisation analysis between aflibercept and bevacizumab. The PBAC considered the issues in the economic models raised by ESC. Given the acceptance of equivalence in efficacy and safety between aflibercept and ranibizumab (paragraph 7.7), the PBAC considered that the primary analysis should be a cost-minimisation to ranibizumab and cost-minimisation to bevacizumab as a secondary analysis. The PBAC noted that the sponsor accepted a 1:1 dose relativity (price parity) to ranibizumab in its Pre-PBAC Response, should ranibizumab become listed on the PBS.

7.12 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, laser photocoagulation and bevacizumab comparisons.

7.13 The PBAC considered the issues in the cost-minimisation analysis between aflibercept and 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 concluded 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.

7.14 The PBAC noted the financial estimates presented in the submission. The PBAC agreed with ESC that the submission's assumption that [redacted] of the population with clinically significant macular oedema has visual impairment is an overestimate. The sponsor in its Pre-PBAC Response agreed that the estimates in the submission were overestimated and presented a sensitivity analysis using lower prevalence rates [redacted]. The PBAC considered that the revised prevalence rates still indicate overestimation.

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

7.16 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).

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	
Severity:	
Condition:	Diabetic macular oedema
PBS Indication:	Diabetic 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: *(to be finalised at a later stage)*	The condition must be due to diabetic macular oedema AND The condition must be diagnosed by fluorescein angiography *AND* *Patient must have documented impairment of best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy study (EDTRS) chart* *AND* *The treatment must be as monotherapy; OR* *The treatment must be in combination with laser photocoagulation*
Definitions	*Visual impairment is defined as best corrected visual acuity score between 73 and 24 letters based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts administered at a distance of 4 meters (approximate Snellen equivalent 20/40-20/320).*
Prescriber Instructions *(to be finalised at a later stage)*	*Treatment must be monthly injections for up to five months followed by 2 mg doses every eight weeks.* *Authority approval for initial treatment of each eye must be sought.* *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 [insert name of form] - PBS Supporting Information Form; and* *c) a copy of the fluorescein angiogram or alternative method of diagnosis where applicable.* *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.* *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.*

Administrative Advice	*Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services* *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* *Written applications for authority prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *GPO Box 9826* *HOBART TAS 7001* *Note* *No increase in the maximum quantity or number of units may be authorised* *Note* *No increase in the maximum number of repeats may be authorised* *Note* *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
AFLIBERCEPT				
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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	
Severity:	
Condition:	Diabetic macular oedema
PBS Indication:	Diabetic 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: *(to be finalised at a later stage)*	The condition must be due to diabetic macular oedema AND The treatment must be as monotherapy; *OR* *The treatment must be in combination with laser photocoagulation* AND Patient must have previously been granted an authority prescription for the same eye
Prescriber instructions *(to be finalised at a later stage)*	*Treatment should be administered every eight weeks and continued until maximum visual acuity is achieved, confirmed by stable visual acuity. Treatment must be ceased when stable visual acuity is achieved.* [Stable visual acuity definition] Patient should be monitored *every eight weeks* for visual acuity following achievement of stable visual acuity. Treatment is resumed with injections every eight weeks when *monitoring indicates vision deterioration* due to DME and continued until stable visual acuity is reached again for <u>three</u> consecutive assessments. The interval between two doses should not be shorter than eight weeks.
Administrative Advice *(to be finalised at a later stage)*	*Authority approvals will be administered by the Complex Drugs Unit of the Department of Human Services* *Authority applications for continuing treatment in the same eye may be made by telephone on 1899 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *<u>Note</u>* *No increase in the maximum quantity or number of units may be authorised* *<u>Note</u>* *No increase in the maximum number of repeats may be authorised* *<u>Note</u>* *Special Pricing Arrangements apply.*

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.