7.6 RANIBIZUMAB, 2.3 mg/0.23 mL injection, 0.23 mL vial, Lucentis®, Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

1.1 The resubmission requested an extension of the current Authority Required listing (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), as diagnosed by fluorescein angiography. The first submission was in March 2013 followed by a resubmission in November 2013.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RANIBIZUMAB 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	Lucentis®	Novartis

Authority required (Section 85)
Initial treatment by an ophthalmologist, of visual impairment due to diabetic macular oedema, as diagnosed by fluorescein angiography. Visual impairment is defined as best corrected visual acuity score between 78 and 39 based on Early Treatment Retinopathy Study (ETDRS)-like VA testing charts administered at a distance of 4 meters (approximate Snellen equivalent 20/32-20/160)

Authority required (Section 85)
Continuing treatment either as monotherapy or in combination with laser photocoagulation by an ophthalmologist, of visual impairment due to diabetic macular oedema, where the patient has previously been granted an authority prescription for the same eye. Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity where visual acuity does not improve by more than 2 letters for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity of 5 letters or more due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than one month.

2.1 As in the November 2013 resubmission, the resubmission sought listing on the basis of superior comparative effectiveness and equivalent comparative safety compared with laser photocoagulation. Although the resubmission claimed that a cost utility analysis was used to support the requested listing, the base case as presented was not able to inform a cost/QALY. This was because the VisQoL instrument relied upon produces estimates within the range of "zero" reflecting blindness rather than death and "one" reflecting best vision rather than best health. An amended cost utility analysis is presented in the commentary.

2.2 The resubmission requested an effective price ($[redacted] that is [redacted]% less than the effective price requested in the November 2013 resubmission ($[redacted]. The resubmission also amended the requested restriction to: allow patients to be treated until their vision stabilises, defined as visual acuity (VA) not improving by more than 2

letters; and retreatment when clinically appropriate, which is defined as a loss of 5 letters or more due to DME.

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

3 Background

3.1 Ranibizumab was registered by the TGA in August 2011 for treatment of visual impairment due to diabetic macular oedema (DME). Ranibizumab also has TGA approval for treatment of neovascular (wet) age-related macular degeneration (AMD) and macular oedema secondary to retinal vein occlusion (RVO). Ranibizumab has been PBS listed for the treatment of patients with wet AMD since August 2007.

3.2 Ranibizumab for the treatment of DME was previously considered at the March 2013 and November 2013 PBAC meetings.

3.3 At the March 2013 meeting, the PBAC rejected the submission on the basis of uncertainty about the ICER, the comparative safety and lack of clarity in the extent of benefit, which was measured as an average difference of five letters on a standard visual acuity chart for the treated eye. The PBAC deferred making a recommendation on the November 2013 resubmission, due to unresolved concerns about the appropriate comparator, and the unsuitability of the submitted model as a basis for determining the cost-effectiveness of ranibizumab in the requested indication.

3.4 The key issues identified in November 2013 PBAC Minutes related to utilities are discussed further below.

3.5 Modelled evaluation – utilities: Paragraph 6.17 – The PBAC recalled its previous concerns about the translation between trial-based VA differences, as measured in treated eyes, and modelled impact on utility for patients. The overall effect will depend on VA in both eyes, and in particular, in the better seeing eye. The resubmission presented revised quality of life estimates based on the VisQoL dimension score. These estimates were calculated for the best seeing eye (BSE) and worst seeing eye (WSE) according to VA state. The resubmission misinterpreted the VisQoL dimension score as a utility value, which resulted in a base case economic analysis incapable of informing an ICER (cost/QALY). Expert advice provided during the evaluation enabled the econometric transformation of the VisQoL dimension score to the AQoL-7D, providing utility values for application in the economic evaluation.

3.6 Modelled evaluation – fundamental misalignment between the design of the model based on treated eye VA and overall patient utilities: Paragraph 6.19 – the PBAC considered that the attempt in the resubmission to adjust for VA across both eyes for the purpose of mapping to utilities does not address the fundamental misalignment in the model. The PBAC also considered that as overall VA is influenced mostly by the better seeing eye, the potential for utility differences to occur is influenced by the proportions of better and worse seeing eyes which are treated (Paragraph 6.21). Data from the RESTORE trial are used to estimate the proportions of patients requiring treatment in the BSE, WSE and both eyes. The resubmission contended that the revised economic model structure will be able to reflect how patients are likely to be treated in the real-world setting. Although the application of VA transition

probabilities based on the treated eye and transformations based on the overall patient (both eyes) remains, it was considered that the adjustments to the model structure through the application of a weighted scenario analysis may partially resolve the misalignment in the economic model.

3.7 Financial estimates – uptake rates: Paragraph 6.25 – use beyond the requested restriction was likely, as interpretation of a response may be higher in clinical practice than in the RESTORE trial, and treatment was likely to be continued in patients with small improvements in vision who would have been classified as non-responders in the RESTORE trial. The resubmission also directly addressed issues raised in the November 2013 DUSC Advice. In reference to the eligible patient pool, the resubmission presented revised estimates from [redacted]% (previous resubmission) to a base case scenario of [redacted]%. Additionally the uptake rates from the DME eligible population had been revised from [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% from Year 1-5 to a progressive rise from [redacted]% in Year 1 to a maximum of [redacted]% in Year 4 and 5. The response rate for initiators had been revised from [redacted]% to [redacted]%. In line with the economic model, the financial estimates assumed a reduced maximum treatment period of [redacted] years.

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

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 As in the November 2013 resubmission, the current resubmission proposed that ranibizumab will replace laser photocoagulation and will be used as first-line treatment for visual impairment due to DME. Off-label bevacizumab, administered via intravitreal injection would also be replaced in practice.

5 Comparator

5.1 As in the November 2013 resubmission, the current resubmission nominated laser treatment as the main comparator.

5.2 In its November 2013 consideration, the PBAC accepted that laser treatment was the appropriate comparator if ranibizumab is used as monotherapy. The PBAC also considered that bevacizumab was a relevant comparator. Bevacizumab was addressed as an additional comparator in the March 2014 minor resubmission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (19), and organisations (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment and improvements in quality of life with ranibizumab, including the following:

- significant improvement in vision with fewer injections;
- ability to lead a normal life and better mobility;
- affordability allows improved financial position to pensioners; and
- safer side effect profile, with a significantly decreased risk of endophthalmitis, compared to bevacizumab.

The comments also noted that the PBAC has sufficient flexibility to determine an appropriate comparator in keeping with QUM principles, and that other countries are reimbursing patients for the cost of ranibizumab for the treatment of DME.

Clinical trials

6.3 Details of the trials presented in the resubmission are provided in the table below.

Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
RESTORE(Trial 2301)	A randomized, double-masked, multicentre, laser-controlled Phase III study assessing the efficacy and safety of ranibizumab (intravitreal injections) as adjunctive and mono-therapy in patients with visual impairment due to diabetic macular edema. 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.	2010 *Ophthalmology,* 2011; 118.4:615-625
DRCR.net Protocol 1 (NCT0044503)	Elman MJ, Aiello LP, Beck RW, Bressler NM, Breslle 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
RIDE (NCT00473382); RISE (NCT00473330)	Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Givson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS. Ranibizumab for Diabetic Macular Edema: Results from 2 Phase III Randomized Trials: RISE and RIDE.	*Ophthalmology.* 2012; 119:789-801
RESOLVE (Trial 2201)	A randomized, double-masked, multicenter, phase II study assessing the safety and efficacy of two concentrations of ranibizumab (intravitreal injections) compared with non-treatment control for the treatment of diabetic macular oedema with center involvement. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, Mitchell P, Sharp D, Wolf-Schnurrbusch UE, Gekkieva M, Weichselberger A, Wolf S. Safety and efficacy of ranibizumab in diabetic macular edema	2008 *Diabetes Care,* 2010, 33:2399-2405

Trial ID	Protocol title/ Publication title	Publication citation
	(RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study.	
READ-2	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. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study.	*Opthalmology*, 2010; 117:2146-2151
REVEAL (NCT00989989)	A randomized, double-masked, multicenter, laser-controlled Phase III study assessing the efficacy and safety of ranibizumab (intravitreal injections) as adjunctive and mono-therapy in patients with visual impairment due to diabetic macular edema	2012
Supplementary studies		
RESTORE 24 month extension study	An open-label, multi-center, 24-month extension study to evaluate the safety of ranibizumab as symptomatic treatment for visual impairment due to diabetic macular edema in patients who have completed the RESTORE trial	2012

Source: Table 10, p23-24 of the resubmission

6.4 The comparative effectiveness and safety of ranibizumab to laser photocoagulation, as both monotherapy and mixed treatment, was informed by the RESTORE and DRCR.net trials. Consistent with the previous resubmission, RIDE, RISE, RESOLVE, READ-2 and REVEAL were appropriately excluded from further consideration. The key features of the included trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in econ model
RESTORE	343	R, DB, MC 12 months	Low	Patients with visual impairment due to diabetic macular oedema	BCVA mean change (letters) from baseline at month 12	Transition probabilities; scenario analyses
DRCR.Net	668 (eyes)	R, DB, MC 12 months	Low			

Abbreviations: BCVA = best corrected visual acuity; DB = double blind; MC = multi-centre; R = randomised
Source: compiled during the evaluation

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

Comparative effectiveness

6.5 As in the March 2013 PBAC consideration, the PBAC accepted that ranibizumab was an effective treatment for visual impairment due to DME, but remained concerned about the extent of clinically relevant improvement in overall BCVA in patients with better VA at baseline (paragraph 7.4, November 2013 PBAC minutes). Key results are summarised in the table below.

Results of BCVA mean change (letters) from baseline at month 12 in the RESTORE and DRCR.net trials

Trial	Ranibizumab		Sham injection
RESTORE [a]	**Sham laser**	**Active laser**	**Active laser**
	N=115	N=118	N=110
Baseline, mean (SD)	64.7 (10.1)	63.4 (10.0)	62.6 (11.0)
At month 12	71.5 (11.8)	69.7 (14.2)	63.4 (14.0)
Mean change (letters) at month 12 (95%CI)	6.8 (5.3, 8.3)	6.4 (4.2, 8.5)	0.9 (-1.3, 3.0)
Comparison vs. Laser, difference in LS means (95% CI)	**6.2 (3.6; 8.7)**	**5.4 (2.4; 8.4)**	NA

Trial	Ranibizumab		Sham injection
RESTORE [a]	**Sham laser**	**Active laser**	**Active laser**
DRCR.net [b]	**Ranibizumab + deferred laser**	**Ranibizumab + prompt laser**	**Sham + prompt laser**
	N(eyes)=188	N(eyes)=187	N(eyes)=293
Baseline, median (25/75th)	66 (58, 72)	66 (55, 72)	65 (56, 73)
Mean change (letters) at month 12 (SD)	9 (12)	9 (11)	3 (13)
Comparison vs. prompt Laser, difference in mean change (95% CI)	**6.0 (3.4; 8.6)**	**5.8 (3.2; 8.5)**	NA

Abbreviations: CI = confidence interval; LS = least-squares; Bolded results are statistically significant

[a] Within the RESTORE trial, laser was administered contemporaneously to intravitreal injection.

[b] Within the DRCR.net trial, prompt laser was administered 1 week (3-10 days) after intravitreal injection and deferred laser was not given until 6 months visit.

Source: Table 24, p73 of the resubmission and Table 11-7, p99 of the RESTORE clinical study report (Technical Document 1 of the resubmission)

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

Comparative harms

6.6 Across the two randomised trials there was a statistically significant increased incidence of conjunctival haemorrhage events in the ranibizumab treatment arm compared to laser (RESTORE: RR = 16.3, 95% CI: 2.04, infinity; DRCR.Net: RR = 9.35, 95% CI: 4.39, 20.07).

6.7 A recent review of systemic adverse events associated with intravitreal VEGF-inhibitors (Campbell et al 2013) indicated that the widespread use of such agents has not resulted in significant increase in the risks of systemic adverse events. For the comparison of ranibizumab vs. bevacizumab, the meta-analyses of CATT and IVAN trials reported no statistically significant differences for arteriothrombotic events (OR = 1.24, 95% CI: 0.62, 2.45).

Benefits/harms

6.8 A summary of the comparative benefits and harms for ranibizumab versus laser treatment (plus sham injection) is presented in the table below.

Summary of comparative benefits and harms for ranibizumab and laser treatment (+sham injection)

Trial	Ranibizumab	Laser	RR^ (95% CI)	Event rate/100 study eyes/patients#		RD^ (95% CI)
				Ranibizumab	Laser	
Benefits						
≥ 10 letters gain (from baseline at 12 months)						
RESTORE	43/115	17/110	2.42 (1.49; 3.99)	37.39	15.45	0.22 (0.11, 0.33)
DRCR.Net	88/188	81/293	1.69 (1.33; 2.15)	46.81	27.65	0.19 (0.10, 0.28)
≥ 10 letters loss (from baseline at 12 months)						
RESTORE	4/115	14/110	0.27 (0.10; 0.76)	3.48	12.73	-0.09 (-0.17, -0.02)
DRCR.Net	6/188	39/293	0.24 (0.11; 0.54)	3.19	13.31	-0.10 (-0.15, -0.05)
Harms						
Conjunctival haemorrhage						
RESTORE	8/115	0/110	16.27 (2.04, infinity)	6.96	0	0.07 (0.03, 0.13)

Trial	Ranibizumab	Laser	RR^ (95% CI)	Event rate/100 study eyes/patients#		RD^ (95% CI)
				Ranibizumab	Laser	
DRCR.Net	42/188	7/293	9.35 (4.39, 20.07)	22.34	2.39	0.20 (0.14, 0.27)

^ RR and RD calculated during the evaluation using Stats Direct 2.7.9.

Benefits reported for study eyes; harms reported for patients

* In Elman 2010, the ocular adverse events of eye pain and visual impairment were grouped under the adverse event headings of sensation/pain, visual symptoms/abnormality and miscellaneous. Given the potential duplication of adverse events included in the miscellaneous category, these were excluded from the assessment of harms.

Source: Compiled during the evaluation

6.9 On the basis of the RESTORE trial, for every 100 patients treated with ranibizumab in comparison to laser:

- approximately 22 additional patients would gain at least 10 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 9 fewer patients would experience a loss of at least 10 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 7 additional patients would experience conjunctival haemorrhage.

6.10 On the basis of the DRCR.Net trial, for every 100 patients treated with ranibizumab in comparison to laser:

- approximately 19 additional patients would gain at least 10 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 10 fewer patients would experience a loss of at least 10 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 20 additional patients would experience conjunctival haemorrhage.

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

Clinical claim

6.11 As for the November 2013 resubmission, the current resubmission describes ranibizumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over laser photocoagulation. The PBAC accepted that ranibizumab is an effective treatment for visual impairment due to DME.

Economic analysis

6.12 The resubmission presented an updated Markov cohort model to evaluate the cost-effectiveness of ranibizumab against laser treatment. In summary, the following revisions have been included in the economic evaluation.

- The proposed effective price has been reduced and MBS unit costs have been updated.
- Updated transformations (VisQoL dimension score) from an existing data set from a large sample of Australian and German patients: revised during the evaluation to more accurately represent utility values for health related quality of life (reflecting all dimensions of quality of life) based on the AQoL-7D. The ESC considered the approach taken in the evaluation has limitations because it was based on an econometric transformation, and noted there is an upper bound to the utility estimates, but, in this case, considered that the approach was reasonable.
- Weighted scenario analysis: the economic model had been adjusted to accommodate a weighted scenario analysis comprising unilateral treatment in the BSE, WSE (weighted between the WSE becoming the BSE or the WSE staying the WSE at 12 months) and bilateral treatment. The final ICER incorporated a

[redacted] distribution across the above scenarios (BSE/WSE - weighted/bilateral). The ESC noted that, in the entire randomised dataset of the RESTORE trial, the treated eye was the BSE in [redacted]% of patients whereas the WSE was treated in [redacted]% of patients. Additionally, [redacted]% of patients had DME in the fellow eye at baseline. Given the extent of bilateral disease, the resubmission appropriately concluded that a significant proportion of bilateral treatment is likely in regular clinical practice.

- Adjustment to all-cause mortality: relationship with low VA and whether the WSE or BSE is affected. The ESC noted that the inclusion of a RR of all-cause mortality of 1.29 may overstate the impact of VA on mortality. In the context of assessing aflibercept for RVO, the July 2013 PBAC meeting considered that a lower hazard ratio than 1.23 reported by Christ et al. (2008) would be more reasonable.
- Inclusion of costs of blindness associated with the BSE VA4 health state and the costs of falls. Disability support pensions (which are transfer payments) were used as a proxy to estimate the costs of resources required when blind. These costs were revised during the evaluation to more appropriately reflect direct health care costs associated with blindness. These revisions were accepted in the Pre-Sub-Committee Response (PSCR).
- Inclusion of costs of falls in the base case, whereas in previous submissions the costs of falls was included only in sensitivity analysis. The ESC was of the view that the use of data from the BMES to estimate the risk of falls associated with VA may favour ranibizumab, as the differences in risk of falls may be attributed to other factors.

Summary of model structure and rationale

Time horizon	15 years in the model base case versus 1 year in the RESTORE trial
Outcomes	Base case: cost/change in VisQoL dimension score Corrected base case: cost/QALY (econometric transformation of the VisQoL dimension score to the AQoL-7D)
Methods used to generate results	Markov cohort expected value analysis
Cycle length	1 month
Transition probabilities	The resubmission assumes that transition probabilities derived from the treated eye (as per the previous November 2013 resubmission) do not differ when patients are treated in the better or worse seeing eye or bilaterally.
Discount rate	5% for costs and outcomes
Software package	Excel 2007

Source: compiled during the evaluation

6.13 The ESC agreed that the structure of the model seems reasonable, but still favoured ranibizumab because of the duration of the model which extrapolates to 15 years and because of the assumption that treatment duration is limited to [redacted] years.

6.14 The key drivers of the model are time horizon, treatment duration and utility transformations for the weighted scenario analysis.

Key drivers of the model

Description	Method/value	Impact
Time horizon	15 years; assumed from 1 year trial duration	High, favours ranibizumab
Treatment duration	Limited to [redacted] years	High, favours ranibizumab
Utility transformations for the weighted scenario analysis	Alternative WSE, BSE and bilateral treatment utilities	High, favours ranibizumab

Source: compiled during the evaluation

6.15 The results of the amended economic evaluation are provided in the table below. These results had been revised to reflect an amended base case incorporating the econometric transformation of the VisQoL to the AQoL-7D and revised costs of blindness.

6.16 The PSCR (p2) acknowledged that the VisQoL scores were not transformed in the resubmission, but did not agree with the transformed utilities proposed by the evaluation as the mapping algorithm tends to under-predict the top end of utility scores resulting in 'implausibly low' utility values for normal vision. The ESC acknowledged that this is a valid criticism of this mapping algorithm, and that this issue can arise because of the data set that informed the mapping, but considered that the mapping approach was reasonable in these circumstances.

Results of the amended economic evaluation

Component	Ranibizumab	Laser treatment	Increment
BSE			
Cost	$ [redacted]	$ [redacted]	$ [redacted]
AQoL-7D: econometric transformation	[redacted]	[redacted]	[redacted]
		Incremental Cost/QALY	$ [redacted]
WSE – where treated eye remains WSE after 12/12			
Cost	$ [redacted]	$ [redacted]	$ [redacted]
AQoL-7D: econometric transformation	[redacted]	[redacted]	[redacted]
		Incremental cost/QALY	$ [redacted]
WSE – where treated eye becomes BSE after 12/12			
Cost	$ [redacted]	$ [redacted]	$ [redacted]
AQoL-7D: econometric transformation	[redacted]	[redacted]	[redacted]
		Incremental cost/QALY	$ [redacted]
WSE – weighted			
Cost	NC		$ [redacted]
AQoL-7D: econometric transformation			[redacted]
		Incremental cost/QALY	$ [redacted]
Bilateral			
Cost	$ [redacted]	$ [redacted]	$ [redacted]
AQoL-7D: econometric transformation	NC		[redacted]
		Incremental cost/QALY	$ [redacted]
Final weighted analysis (amended economic evaluation)			
Cost	NC		$ [redacted]
AQoL-7D: econometric transformation			[redacted]
Overall incremental cost/QALY (amended base case)			**$** [redacted]

Note: The econometric transformation of the VisQoL dimension score to the AQoL-7D was conducted during the evaluation. Additionally, the costs associated with blindness were updated during the evaluation to more appropriately reflect direct health care related costs.

Abbreviations: BSE = best seeing eye; NC = not calculable; WSE = worse seeing eye

Source: Constructed during the evaluation

6.17 The base case ICER of the amended model, (range $45,000/QALY to $75,000/QALY), is greater than the ICER of $15,000/QALY - $45,000/QALY presented in the resubmission considered in November 2013. The November 2013 PBAC considered that model unsuitable as a basis for determining the cost-effectiveness of ranibizumab in the treatment of DME (paragraph 6.20).

6.18 In March 2007, the PBAC recommended the listing of ranibizumab for the treatment of subfoveal choroidal neovascularisation due to AMD on the basis of acceptable cost effectiveness informed by an ICER of $15,000/QALY to $45,000/QALY. Based

on the amended economic model, a ranibizumab price of $[redacted] would be required to achieve an equivalent ICER.

6.19 The results of the sensitivity analyses indicate that the model was most sensitive to the time horizon, treatment duration and utility assumptions:

- the reduction of the timeframe of the model to [redacted] years (consistent with the ranibizumab AMD submission, March 2007) results in an ICER of $105,000/QALY - $200,000/QALY
- the continuation of treatment from year [redacted] of the model, applying usage assumptions from year [redacted], results in an ICER of $75,000/QALY – 105,000/QALY
- the application of alternative BSE, WSE and bilateral treatment utilities (informed by the econometric transformation of the VisQoL dimension score to the AQoL-7D) results in an ICER of $75,000/QALY - $105,000/QALY.

6.20 The ESC cited another source for all-cause mortality (Christ et al, 2008) and noted the need for consistency of comparable inputs across corresponding models for ranibizumab and aflibercept. The ESC therefore respecified the base case as detailed below:

- excess mortality risk reduced to RR=1.13 (the smaller RR from Christ et al, 2008)
- risk and cost of falls removed
- cost of blindness removed.

The ESC also specified additional sensitivity analyses:

- mortality set to RR=1.13 and falls excluded but blindness costs included
- mortality set to RR=1.00, falls excluded and cost of blindness excluded.

The results are presented in the table below.

Results of model amended according to the ESC specifications

Analyses		Incremental costs	Incremental QALYs	Cost/QALY
Evaluation base case		$[redacted]	[redacted]	$[redacted]
ESC base case	**Mortality risk to Christ 2008 (RR=1.13); risk and cost of falls removed; cost of blindness removed.**	**$[redacted]**	[redacted]	**$[redacted]**
ESC analysis	Mortality risk to Christ 2008 (RR=1.13); risk and cost of falls removed.	$[redacted]	[redacted]	$[redacted]
ESC analysis	Mortality risk removed (RR=1.00); risk and cost of falls removed; cost of blindness removed.	$[redacted]	[redacted]	$[redacted]

6.21 The PBAC noted that the Pre-PBAC Response (p2) presented alternative approaches to mapping utility values using alternative AQoL-7D and trial-based EQ-5D values as a basis for alternative ICERs that were less than that accepted by the PBAC for AMD (range $15,000/QALY to $45,000/QALY). The PBAC considered that these alternative ICERs for DME could not be verified independently, including with reference to the accompanying spreadsheets. For the alternative AQoL-7D utility values, which was based on varying the answers to Question 18 ("How well can you see?") in the instrument, there was limited information about what assumptions were made for responses to all questions in the instrument, and the basis for these assumptions, which has an effect on the utilities generated. For the corresponding ICER and all other ICERs presented in the Pre-PBAC Response, there was also no indication as to how the sponsor updated the model to include the reduced cost of blindness, beyond the fact that the Pre-PBAC Response appeared to be able to replicate the evaluation base case in this regard.

6.22 The PBAC considered the issues in the economic model had been addressed as far as possible, but noted that there were still some uncertainties about the best basis for estimating utilities and accepted that it was reasonable for the Pre-PBAC Response to have some debate about this. The PBAC agreed with the ESC that the econometric transformation undertaken in the evaluation was a reasonable basis for the model. The PBAC agreed with the ESC that this transformation was limited by having an upper bound to the utility estimates due to the data set that informed the mapping. However, the alternative sources from the literature identified in the Pre-PBAC Response were less consistent with the range of utilities reported in the RESTORE trial because they generated wider utility ranges across the identified health states.

6.23 The PBAC reviewed three other aspects of the model: costs of blindness, costs of falls and relative risk of mortality, noting the varying positions between the evaluation, the ESC advice (see table above) and its own position (see table below). The PBAC considered that, consistent with accepting consequences for utilities following the use of ranibizumab, it would be reasonable to accept some consequences for the costs of blindness and reduction in mortality. However, the PBAC considered that these consequences were overestimated in the submission and so instead accepted the reduced estimates in the PBAC base case below, noting also that they were more consistent with these parameters in other models it has reviewed for this condition. The PBAC noted that the estimated consequences for falls had little effect on the ICERs.

Ranibizumab sensitivity analyses

Analyses	Variables			Inc. costs	Inc. QALY	Cost/ QALY
	Cost of blindness	Cost of falls	Mortality			
Evaluation base case	Reduced (Clarke 2008)	Included	RR = 1.32 (BMES)	$[redacted]	[redacted]	$[redacted]
PBAC analysis 1 (remove cost of falls only)	Reduced (Clarke 2008)	$[redacted]	RR = 1.32 (BMES)	$[redacted]	[redacted]	$[redacted]
PBAC analysis 2 (reduce RR mortality only)	Reduced (Clarke 2008)	Included	RR = 1.13 (Christ 2008)	$[redacted]	[redacted]	$[redacted]
PBAC base case (remove cost of falls and reduce RR of mortality)	**Reduced (Clarke 2008)**	**$[redacted]**	**RR = 1.13 (Christ 2008)**	**$[redacted]**	**[redacted]**	**$[redacted]**

6.24 The PBAC agreed that, at its revised base case ICER in the range of $45,000/QALY - $75,000/QALY, ranibizumab for DME was not acceptably cost-effective. The PBAC considered that ranibizumab would be cost-effective at a reduced price that produced an ICER of between $15,000/QALY and $45,000/QALY, similar to that previously accepted for ranibizumab in the treatment of AMD.

Drug cost/patient/year

6.25 The drug cost/patient/year was estimated to be less than $10 million in Year 1 for responders, $[redacted] in Year 2 and $[redacted] in Year 3 for continuations; $[redacted] in Year 1 for non-responders.

6.26 For treatment responders in the first year of treatment, the drug cost/year is $[redacted] based on [redacted] injections. Continuing into the second year of treatment, drug cost/year decreases to $[redacted] based on [redacted] injections. In the third year of treatment, the cost per patient is $[redacted] based on [redacted] injections. For non-responders, the drug/cost during the first year is $[redacted] based on [redacted] injections.

Estimated PBS usage & financial implications

6.27 This resubmission was not considered by DUSC. The likely number of patients treated per year was estimated in the submission to be between 100,000 to 200,000 in year 5, at an estimated cost to Government of $30 to $60 million in year 5.

Estimated use and financial implications compared to previous submissions

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated - Nov 2013					
Uptake rate					
Uptake rate - Nov 2013					
Injections					
Injections - Nov 2013					
Estimated net cost to PBS/MBS					
Net cost to PBS	$	$	$	$	$
Net cost to PBS - Nov 2013	$	$	$	$	$
Net cost to MBS	$	$	$	$	$
Net cost to MBS - Nov 2013	$	$	$	$	$
Estimated total net cost					
Net cost PBS/MBS	**$**	**$**	**$**	**$**	**$**
Net cost PBS/MBS - Nov 2013	$	$	$	$	$
Net cost PBS/MBS - March 2013	$	$	$	$	$

Source: Compiled during the evaluation

6.28 Due to an increase in estimated patients with visual impairment (% of DME patients compared to % in November 2013); increased uptake rates; and an increased response rate in initiators (% compared to % in November 2013), the estimated net cost to government of $ over the first 5 years of listing has increased considerably compared to the November 2013 estimate of $.

6.29 The resubmission applied a maximum treatment duration for a patient of years in the financial estimates . This was inconsistent with the requested restriction as there was no definitive stopping rule. Therefore the total net cost to government was likely to be underestimated as treatment duration may extend beyond years.

Quality use of medicines

6.30 As in the November 2013 resubmission, the current resubmission stated that the sponsor has detailed pharmacovigilance and risk minimisation activities in the risk management plan.

Financial management – risk sharing arrangements

6.31 As in the November 2013 resubmission, the current resubmission indicated the sponsor is seeking to enter a risk-sharing arrangement (RSA). No details of the proposed RSA were provided.

6.32 The PBAC noted the sponsor's willingness to enter into a risk sharing arrangement (RSA) and, in the absence of any detail proposed by the sponsor, recommended that the Government and sponsor enter into a RSA to reduce uncertainty with regard to utilisation estimates and cost of ranibizumab to the PBS. The PBAC considered that

the reduced price of ranibizumab at the recommended ICER between $15,000/QALY and $45,000/QALY and the estimated population would become the basis of the risk-sharing arrangement. The PBAC recommended that Government expenditure above any subsidisation cap/s should be a 100% rebate. The PBAC also recommended that the Department consider how best to implement the sponsor's offer in the Pre-PBAC Response to address the uncertainty of treatment beyond [redacted] years in the RSA.

7 PBAC Outcome

7.1 The PBAC recommended extending the listing of ranibizumab as Section 85 Authority required benefit to include treatment of visual impairment due to DME. The PBAC considered that authority applications through the PBS and Specialised Drugs Branch of the Department of Human Services would be appropriate for ranibizumab, similar to administrative arrangements for ranibizumab and aflibercept in AMD.

7.2 The PBAC noted the clinical place for ranibizumab would be used as treatment of visual impairment due to DME. The PBAC recalled its previous consideration from the November 2013 PBAC meeting that it was likely that ranibizumab would replace a proportion of bevacizumab use across multiple treatment settings.

7.3 The comparator of laser treatment had previously been accepted by the PBAC as the appropriate comparator if ranibizumab is used as monotherapy. The PBAC noted the issue with bevacizumab as an additional comparator was addressed in the March 2014 minor resubmission and so did not focus on this comparison.

7.4 The PBAC's views on ranibizumab's comparative benefits and harms remained unchanged from those formed in November 2013.

7.5 The PBAC considered the issues in the economic model had been addressed as far as possible, in particular the relationship between the assessment of effects on the treated eye in the trials and the generation of utility consequences for the whole person, but noted that there were still some uncertainties about the best basis for estimating utilities. The PBAC agreed with the ESC that the econometric transformation undertaken in the evaluation was a reasonable basis for its revised base case ICER in the range of $45,000/QALY to $75,000/QALY, after further adjusting for costs of blindness, costs of falls and relative risk of mortality.

7.6 The PBAC noted the revised estimated net cost to the government in the resubmission has increased in comparison to the November 2013 estimate as a consequence of following previous DUSC advice. The PBAC considered that the approach taken by the resubmission was reasonable.

7.7 The PBAC noted the comment in the Pre-PBAC Response (p4) that some of the results from the clinical evidence were not statistically significant, particularly the results for eye pain and visual impairment, and therefore agreed that non-statistically significant results could be removed from the benefits and harms summary.

7.8 The PBAC noted that the sponsor is cooperating with MSAC in analysing its trial data to explore the clinical utility of optical coherence tomography (OCT) in relation to the use of ranibizumab. The PBAC recommended that the Department should consider ensuring that that this would continue after implementing the extended PBS listing by including this in the proposed Deed of Agreement with the sponsor.

7.9 Advice to the Minister under subsection 101(3BA) of the *National Health Act 1953*
In accordance with subsection 101(3BA) of the *National Health Act 1953*, the PBAC advised that it is of the opinion that, on the basis if the material available to it at its July 2014 meeting, ranibizumab should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

7.10 The PBAC advised that ranibizumab is not suitable for prescribing by nurse practitioners.

7.11 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 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	
RANIBIZUMAB Ranibizumab 2.3 mg/0.23 mL injection, 1 x 0.23 mL vial	1	2	Lucentis	NV

Condition:	Visual impairment
Treatment phase:	Initial treatment
Restriction:	Authority Required
Treatment criteria:	Must be treated by an ophthalmologist
Clinical criteria:	The condition must be due to diabetic macular oedema AND The condition must be diagnosed by fluorescein angiography 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 78 and 39 letters based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts administered at a distance of 4 metres (approximate Snellen equivalent 20/32-20/160).

Prescriber Instructions	*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* *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.* *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.*

Condition:	Visual impairment
Treatment phase:	Continuing treatment

Restriction:	Authority Required
Treatment criteria:	Must be treated by an ophthalmologist
Clinical criteria:	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	*Treatment should be administered monthly 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 is where visual acuity does not improve by more than *2 letters for three consecutive monthly assessments* performed while on ranibizumab treatment. Patient should be monitored monthly for visual acuity following achievement of stable visual acuity. Treatment is resumed with monthly injections when monitoring indicates *a loss of visual acuity of 5 letters or more d*ue to DME and continued until stable visual acuity is reached again for three consecutive assessments. The interval between two doses should not be shorter than one month.
Administrative Advice	*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).* *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.*

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

Novartis are happy that in granting ranibizumab in DME a positive recommendation the PBAC see the benefit of treating patients in this setting. Novartis are pleased to have worked through the outstanding modelling issues with the Department of Health to an acceptable solution. Novartis does not agree with ESC and the PBAC regarding the final utility values used to calculate the incremental cost effectiveness ratio (ICER) of ranibizumab, as these values were calculated using an algorithm with clear limitations (acknowledged in the ESC advice and the PBAC at this meeting). Further, the final values are not reflective of consistent with several other published sources (Brown 1999, Czoski-Murray et al. 2009, Heintz et al. 2012) as well as assumptions from RESTORE. Novartis will continue working collaboratively with the Department of Health to bring access to Australian patients as soon as possible.