7.7 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 re-submission requested an extension of the current Authority Required listing of ranibizumab (for treatment of subfoveal choroidal neovascularisation due to age-related macular degeneration) to include initial and continuing treatment, by an ophthalmologist, of a patient with visual impairment due to macular oedema secondary to retinal vein occlusion (both branch retinal vein occlusion and central retinal vein occlusion). The first submission was in November 2012 followed by a re-submission 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 macular oedema secondary to branched retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

For BRVO, visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) in the eye proposed for treatment
For CRVO, visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/40 to 20/320 (Snellen equivalent) in the eye proposed for treatment

Authority required (Section 85)
Continuing treatment by an ophthalmologist, of visual impairment due to macular oedema secondary to retinal vein occlusion, where the patient has previously been granted an authority prescription.

Treatment is given monthly for six months. Consideration should be given to ceasing treatment if no response is seen after 3-4 injections. Thereafter, treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular oedema secondary to RVO (i.e. patient's BCVA is 20/40 or worse (Snellen equivalent) using ETDRS charts). Treatment is continued until stable visual acuity is reached for three consecutive monthly assessments.

2.1 The current re-submission made the same claim as in the November 2013 re-submission: that ranibizumab has superior effectiveness with a similar safety profile compared to the standard of care (laser treatment in BRVO and observation in CRVO). Although the re-submission 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 ESC noted that the following details of the restriction would need to be resolved should PBAC recommend listing: the level of detail provided from the Product Information document; the frequency of injections; whether a maximum number of injections or maximum duration of treatment is specified; whether these specifications are related to measurement of visual acuity (VA); and if so, how and when; and the role (or not) of optical coherence tomography (OCT).

2.3 The re-submission requested an effective price ($[redacted]) that is [redacted]% less than the effective price requested in the November 2013 re-submission ($[redacted]).

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

3 Background

3.1 Ranibizumab was approved by the TGA for treatment of visual impairment due to macular oedema secondary to RVO following the 280th ACPM meeting on 6th and 7th of October 2011. Ranibizumab also has TGA approval for treatment of neovascular (wet) age-related macular degeneration (AMD) and was also TGA registered in August 2011 for treatment of visual impairment due to diabetic macular oedema (DME). Ranibizumab has been PBS listed for the treatment of patients with wet AMD since August 2007.

3.2 Ranibizumab was previously considered for the treatment of RVO at the November 2012 and November 2013 PBAC meetings.

3.3 At the November 2012 meeting, the PBAC rejected the submission on the basis of uncertainty about the ICER, which was likely to be an underestimate. The PBAC deferred making a recommendation in relation to the November 2013 re-submission 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 re-submission 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 re-submission 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 re-submission to adjust for VA across both eyes for the purpose of mapping to utilities did 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 BRAVO and CRUISE trials are used to estimate the proportions of patients requiring treatment in the BSE, WSE and both eyes. The re-submission 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.

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

4 Clinical place for the proposed therapy

4.1 RVO is a blockage of the vessel which drains blood out of the retina, the light-sensitive tissue at the back of the eye. The blockage results in increased pressure within the blood vessel causing blood and fluid to leak from the blood vessels into the retinal potentially leading to macular oedema. Occlusions are categorised into branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). The current recommended treatment for BRVO patients with macular oedema and vision impairment is laser photocoagulation. For patients with CRVO current treatment is observation only.

4.2 Ranibizumab will likely either replace or be co-administered with laser treatment in BRVO patients and replace observation in CRVO patients. Off-label bevacizumab, administered via intravitreal injection would also be replaced in practice.

5 Comparator

5.1 As in the November 2013 re-submission, the current re-submission nominated laser photocoagulation and observation for patients with BRVO and observation only for patients with CRVO as comparators.

5.2 As in November 2012, in its November 2013 consideration the PBAC considered that bevacizumab was a relevant comparator. Bevacizumab was addressed as an additional comparator in the March 2014 minor re-submission.

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 (7), health care professionals (19), and organisations (4) 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 Lucentis for the treatment of RVO.

Clinical trials

6.3 The re-submission presented the same two trials presented in the November 2012 and November 2013 submissions, comparing ranibizumab to sham injection in BRVO (BRAVO) and CRVO (CRUISE).

6.4 Details of the trials presented in the re-submission are provided in the table below.

Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Trial FVF4165g (BRAVO)	A phase III, multicentre, randomised, sham injection-controlled study of the efficacy and safety of Ranibizumab injection compared with sham in patients with macular oedema secondary to branch retinal vein occlusion.	Final report July 2010
	Campochiaro, PA, Heier, JS, Feiner, L, et al. Ranibizumab for Macular Oedema following Branch Retinal Vein Occlusion: Six-month Primary end Point Results of a Phase III Study.	Ophthalmology, 2010; Vol 117(6): 1102-12.
	Brown DM, Campochiaro PA, Bhisitkul RB et al. Sustained Benefits from Ranibizumab for Macular Oedema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study.	Ophthalmology, 2011; Vol 118(8):1594-1602
Trial FVF4166g (CRUISE)	A phase III, multicentre, randomised, sham injection-controlled study of the efficacy and safety of Ranibizumab injection compared with sham in patients with macular oedema secondary to central retinal vein occlusion.	Final Report August 2010
	Brown, DM, Campochiaro, PA, Singh, RP, et al. Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Six-Month Primary End Point Results of a Phase III Study.	Ophthalmology, 2010; Vol 117(6): 1124-33
	Campochiaro PA, Brown DM, Awh CC et al. Sustained Benefits from Ranibizumab for Macular Oedema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study.	Ophthalmology 2011; Vol 118(10): 2041-2049
Supplementary randomised trial		
Trial FVF3426g (HORIZON)	An open-label, multicentre extension study to evaluate the safety and tolerability of ranibizumab in subjects with macular oedema secondary to retinal vein occlusion (RVO) who have completed a Genentech-sponsored ranibizumab study (either BRAVO or CRUISE).	May 2011
	Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, et al. Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Long-term Follow-up in the HORIZON trial.	Ophthalmology, 2012; Vol 119(4): 802-809

Source: Table 9, 36 -39 of the re-submission

6.5 The key features of the BRAVO and CRUISE trials are summarised in the table below. Rescue laser treatment was offered to both arms of the BRAVO trial.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in econ model

BRAVO	N=397	R, DB, MC 12 months	Low	Patients with visual impairment due to macular oedema secondary to RVO	BCVA mean change (letters) from baseline at month 12	Transition probabilities; scenario analyses
CRUISE	N=392	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

6.6 The PBAC accepted that ranibizumab is an effective treatment for visual impairment due to RVO, but remained concerned regarding the extent of clinically relevant improvement in overall BCVA (paragraph 6.7, November 2013 PBAC Minutes). Key results are summarised in the table below.

Results of BRAVO and CRUISE trials

Change in BCVA	SHAM	Ranibizumab 0.5mg		Ranibizumab 0.3mg	
	Change from baseline	Change from baseline	Difference vs. sham	Change from baseline	Difference vs. sham
BRAVO	N=132 7.3 (5.1, 9.5)	N=131, 18.3 (16.0, 20.6)	10.6 (7.6, 13.6)	N=134 16.6 (14.7, 18.5)	9.4 (6.6, 12.2)
CRUISE	N=130 0.8 (-2.0, 3.6)	N=130 14.9 (2.6, 17.2)	13.8 (10.3,17.4)	N=132 12.7 (9.9; 15.4)	11.5 (7.7, 15.3)

BCVA=best corrected visual acuity
Source: Table 21, p84 of the re-submission

6.7 During the evaluation, one publication (Campochiaro et al 2014) was found describing the RETAIN study (N=66), which followed a patient subset of the HORIZON study. The RETAIN study suggests that a significant portion (56% in CRVO; 50% in BRVO) of patients continued injections after 4 years. However, the sponsor notes that this group of patients is a small subset of the two main trials, and it may or may not represent likely duration of treatment in the Australian setting.

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

Comparative harms

6.8 In the BRAVO trial, there was a statistically significant increase in occurrence of conjunctival haemorrhage (RR=1.30; 95%CI 1.01, 1.69) and retinal exudates (RR=1.79; 95%CI; 1.07, 3.02) in the ranibizumab treatment arm compared to sham.

6.9 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

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

Summary of comparative benefits and harms for ranibizumab and sham

Trial	Ranibizumab	Sham	RR*	Event rate/100 study eyes/patients^	RD*

	0.5mg	Injection	(95% CI)	Ranibizumab	Sham Injection	(95% CI)
Benefits						
Gain ≥ 15 letters at 12 months						
BRAVO (BRVO)	79/131	58/132	1.37 (1.09, 1.75)	60.3	43.9	0.16 (0.04, 0.28)
CRUISE (CRVO)	66/130	43/130	1.53 (1.15, 2.08)	50.8	33.1	0.18 (0.06, 0.29)
Loss < 15 letters at 12 months						
BRAVO (BRVO)	128/131	124/132	1.04 (0.99, 1.11)	97.7	93.9	0.04 (-0.01, 0.27)
CRUISE (CRVO)	127/130	117/130	1.09 (1.02, 1.17)	97.7	90.0	0.08 (0.02, 0.14)
Harms						
Conjunctival haemorrhage						
BRAVO (BRVO)	71/130	55/131	1.30 (1.01, 1.69)	54.6	42.0	0.13 (0.006, 0.244)
CRUISE (CRVO)	53/129	42/129	1.26 (0.92, 1.75)	41.1	32.6	0.09 (-0.033, 0.201)
Retinal exudates						
BRAVO (BRVO)	32/130	18/131	1.79 (1.07, 3.02)	24.6	13.7	0.11 (0.013, 0.205)
CRUISE (CRVO)	22/129	15/129	1.47 (0.81, 2.69)	17.1	11.6	0.05 (-0.032, 0.142)

* RR and RD calculated during the evaluation using Stats Direct Version 2.7.9
^ Benefits reported for study eyes; harms reported for patients
Abbreviations: RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation/

6.11 On the basis of the two trials presented by the re-submission, for every 100 patients treated with ranibizumab in comparison to laser/sham injection:

- approximately 16 to 18 additional patients would gain at least 15 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 4 to 8 additional patients would experience a loss of less than 15 letters in visual acuity in the studied eye (from baseline to 12 months)
- approximately 9 to 13 additional patients would experience conjunctival haemorrhage
- approximately 5 to 11 additional patients would experience retinal exudates.

Clinical claim

6.12 The re-submission made the same claim as made in the November 2012 and 2013 submissions, that ranibizumab has superior effectiveness with a similar safety profile compared to the standard of care (laser treatment in BRVO and observation in CRVO). The PBAC accepted that ranibizumab is an effective treatment for visual impairment due to RVO.

Economic analysis

6.13 The re-submission presented an updated Markov cohort model to evaluate the cost-effectiveness of ranibizumab against laser treatment for BRVO and observation for CRVO. 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 evaluate separately 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 in a sensitivity analysis. The final base case ICER incorporated a [redacted] distribution across the above scenarios (BSE/WSE - weighted).
- 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 the same indication, 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	10 years in the model base case versus 6 months in the BRAVO and CRUISE trials
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; half cycle correction is applied
Transition probabilities	The re-submission assumes that monthly transition probabilities derived from the treated eye (as per the previous November 2013 re-submission) do not differ when patients are treated in the better or worse seeing eye.
Discount rate	5% for costs and outcomes
Software package	Excel 2007

Source: compiled during the evaluation

6.14 The ESC agreed that the structure of the model seems reasonable, but still favoured ranibizumab because it extrapolates from 12 month trial data to 10 years, and assumes that treatment duration will be limited to [redacted] years.

6.15 A summary of the key drivers of the model is time horizon, treatment duration and utility transformations for the weighted scenario analysis.

Key drivers of the model

Description	Method/value	Impact
Time horizon	10 years extrapolated from 6 month treatment phase and 6 month observation phase in trials.	High, favours ranibizumab
Utility transformations for the	Alternative WSE, BSE and bilateral treatment utilities.	High, favours ranibizumab

Description	Method/value	Impact
weighted scenario analysis		
Treatment duration	Limited to [redacted] years	High, favours ranibizumab

Source: compiled during the evaluation

6.16 The results of the amended economic evaluation for BRVO weighted, CRVO weighted and the overall final weighted ICER 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.

6.17 The Pre-Sub-Committee Response (PSCR) (p2) acknowledged that the VisQoL scores were not transformed in the re-submission, 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 – BRVO, CRVO weighted and overall

Component	Ranibizumab	Laser/sham	Increment
BRVO weighted			
Cost	NC		$[redacted]
AQoL-7D: econometric transformation			[redacted]
		Incremental cost/QALY	$[redacted]
CRVO weighted			
Cost	NC		$[redacted]
AQoL-7D: econometric transformation			[redacted]
		Incremental cost/QALY	$[redacted]
Final weighted analysis BRVO and CRVO (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.

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

6.18 The base case ICER of the amended model was in the range of $75,000/QALY - $105,000/QALY and greater than the ICER in range of $15,000/QALY - $45,000/QALY presented in the re-submission 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 RVO (paragraph 6.18).

6.19 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.

6.20 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 for [redacted] additional years, applying usage assumptions from year [redacted], results in an ICER of $105,000/QALY- $200,000/QALY
- the application of WSE utilities (informed by the econometric transformation of the VisQoL dimension score to the AQoL-7D) which hold the effect of the BSE constant, results in an ICER of $105,000/QALY- $200,000/QALY.

6.21 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]

6.22 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 close to that accepted by the PBAC for AMD (range of $15,000/QALY to $45,000/QALY. The PBAC considered that these alternative ICERs for RVO 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.

6.23 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.

6.24 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 utility 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.

6.25

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 = 1.29 (Karpa 2009)	$[redacted]	[redacted]	$[redacted]
PBAC analysis 1 (remove cost of falls)	Reduced (Clarke 2008)	$[redacted]	RR = 1.29 (Karpa 2009)	$[redacted]	[redacted]	$[redacted]
PBAC analysis 2 (reduce RR mortality)	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]

6.26 The PBAC agreed that, at its revised base case ICER in range of $75,000/QALY to 105,000/QALY, ranibizumab for RVO 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. The PBAC noted that it would need a substantial price reduction in order to reach this ICER.

Drug cost/patient/year

6.27 The drug cost/patient/year was estimated to be $[redacted] in Year 1 for BRVO responders and $[redacted] for CRVO responders; $[redacted] in Year 2 for BRVO continuations and $[redacted] for CRVO continuations; $[redacted] in Year 3+ for both BRVO and CRVO continuations; $[redacted] in Year 1 for BRVO and CRVO non-responders.

6.28 The above costs assume [redacted] and [redacted] injections in the first year for BRVO and CRVO respectively, [redacted] and [redacted] injections in Year 2 for BRVO and CRVO respectively, and 2 per year for the remaining 2 years for both BRVO and CRVO. Non-responders are assumed to use [redacted] injections.

Estimated PBS usage & financial implications

6.29 This re-submission was not considered by DUSC. The likely number of patients treated per year was estimated in the submission to be between 10,000 to 50,000 in year 5, at an estimated cost to Government of $20 to $30 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					
Number treated - Nov 2012					
Uptake rate BRVO/CRVO					
Uptake rate - Nov 2013					
Uptake rate - Nov 2012					
Injections [a]					
Injections - Nov 2013[a]					
Injections - Nov 2012[a]					
Estimated net cost to PBS/MBS					
Net cost to PBS	$	$	$	$	$
Net cost to PBS - Nov 2013	$	$	$	$	$
Net cost to PBS- Nov 2012	$	$	$	$	$
Net cost to MBS	$	$	$	$	$
Net cost to MBS - Nov 2013	$	$	$	$	$
Net cost to MBS - Nov 2012	$	$	$	$	$
Estimated total net cost					
Net cost PBS/MBS	**$**	**$**	**$**	**$**	**$**
Net cost PBS/MBS - Nov 2013	$	$	$	$	$
Net cost to PBS/MBS - Nov 2012	$	$	$	$	$

[a] Adjusted for bilateral use

Source: Compiled during the evaluation

6.30 Methods for calculating the eligible population have changed since the November 2013 re-submission. The re-submission estimated the prevalent pool prior to listing with an incidence rate and calculated uptake rates for Year 1 in the prevalent pool based on an incidence rate. This reduced the estimated eligible population significantly but increased the treated population considerably. The re-submission appeared to have combined incident populations across 2 years to estimate the eligible population, and has used incidence rates that cannot be verified. Overall, the re-submission's estimates did not appear to be accurate. The ESC considered that the approach taken by the re-submission was reasonable and that using the incidence rate for estimating the prevalent pool of patients prior to Year 1 of listing is appropriate.

6.31 Uptake rates for all years increased since the November 2013 re-submission. The change in eligible patient population and uptake rates resulted in an increased of estimated net cost to the government of $ over the first 5 years of listing compared to the $ estimated in the November 2013 re-submission. This increase was not likely to be reasonable, given the methods used to calculate eligible and treated patients. The ESC considered that the approach taken by the re-submission was reasonable as a consequence of following previous DUSC advice in the context of DME.

Quality use of medicines

6.32 As in the November 2013 re-submission, the current re-submission states that the sponsor has detailed pharmacovigilance and risk minimisation activities in the risk management plan.

Financial management – risk sharing arrangements

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

6.34 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 macular oedema secondary to retinal vein occlusion (both branch retinal vein occlusion and central retinal vein occlusion). 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 likely either replace or be co-administered with laser treatment in BRVO and replace observation in CRVO patients. 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 As in November 2013 PBAC meeting, the PBAC accepted that laser photocoagulation + observation for patients with BRVO and observation only for patients with CRVO were the appropriate comparators. The PBAC noted the issue with bevacizumab as an additional comparator was addressed in the March 2014 minor re-submission 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 of $75,000/QALY - $105,000/QALY, after further adjusting for costs of blindness, costs of falls and relative risk of mortality.

7.6 The PBAC agreed with the ESC that the approach taken by the re-submission in calculating the estimated population was reasonable and that using the incidence rate for estimating the prevalent pool of patients prior to Year 1 of listing is appropriate. The PBAC considered that the approach taken by the re-submission to

estimate uptake rates and estimated net cost to government were reasonable as a consequence of following previous DUSC advice in the context of DME.

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 result for eye pain, 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 macular oedema secondary to branched retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) *AND* *The condition must be diagnosed by [appropriate diagnostic method]* *AND* *The treatment must be the sole PBS-subsidised therapy for this condition.*
Definitions	For BRVO, visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) in the eye proposed for treatment For CRVO, visual impairment is defined as best-corrected visual acuity using ETDRS charts of 20/40 to 20/320 (Snellen equivalent) in the eye proposed for treatment
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 [appropriate diagnostic report].* *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 [appropriate diagnostic test] 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 [alternative 1 or alternative 2].* *A patient is eligible for a total of 12 subsidised treatments per eye (3 initial plus 9 continuing).*

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 macular oedema secondary to branched retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) AND Patient must have previously been granted an authority prescription for the same eye *AND* *The treatment must be the sole PBS-subsidised therapy for this condition.*

Prescriber Instructions	Treatment ~~is given~~ *should be administered* monthly for six months. Consideration should be given to ceasing treatment if no response is seen after 3-4 injections. Thereafter, treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular oedema secondary to RVO (ie patient's BCVA is 20/40 or worse (Snellen equivalent) using ETDRS charts). Treatment is continued until stable visual acuity is reached for three consecutive monthly assessments. *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.* *The interval between two doses should not be shorter than one month* *A patient is eligible for a total of 12 subsidised treatments per eye (3 initial plus 9 continuing).*
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 1800 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.