- Please note that the Premeeting briefing was prepared before publication of the RADIANCE and REPAIR trials, therefore, some of the redacted information in this report is no longer confidential.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ranibizumab for treating choroidal neovascularisation associated with pathological myopia

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- The manufacturer explained that it did not include bevacizumab as a comparator as it is not licensed for use in the UK for choroidal neovascularisation (CNV) associated with pathological myopia. The manufacturer claims that bevacizumab is not established practice in the UK, however the professional and patient groups maintain that bevacizumab is used in the UK for this indication, and that it is more likely to be used than verteporfin photodynamic therapy (vPDT). Is it appropriate for the manufacturer to exclude bevacizumab as a comparator, despite it being listed as a comparator in the scope for this appraisal?

Clinical effectiveness

- The primary endpoint in the Novartis phase III trial (RADIANCE) which compared ranibizumab with verteporfin photodynamic therapy (vPDT) is limited to 3 months. The ERG noted that other studies in this clinical area have used 12 months. They expressed concerns that 3 months is insufficient for assessing visual acuity since it does not provide data on longer term gain or deleterious effects of treatment. Is the primary outcome duration appropriate?

- The Novartis phase III trial (RADIANCE) did not assess the potential development of geographic atrophy following ranibizumab. The development of geographical atrophy at the macula could affect long-term visual outcomes. Is it appropriate for the manufacturer not to include this as an outcome?

Cost effectiveness

- The health economic model uses effectiveness data for ranibizumab from the Novartis phase III trial and for vPDT from the VIP trial. These data are not balanced in terms of the proportion of patients presenting with non-subfoveal involvement which may result in an inflated effect of the benefit of ranibizumab. Could the different proportions of non-subfoveal involvement in the ranibizumab and vPDT populations have affected the health economic model?
- The health economic model accounts for the possibility of the better-seeing eye (BSE) becoming the worse-seeing eye (WSE), or vice versa, as patients change health states. The ERG noted that, while change from BSE to WSE and vice versa will occur, the method used by the manufacturer seems to underestimate the net QALY gains and costs of blindness that may arise from the more effective treatment. Does the economic model appropriately account for changes in the BSE or WSE in estimating QALY gains and costs of blindness?
- The manufacturer did not use EQ-5D data from the Novartis phase III trial but used health related quality of data from Czoski-Murray et al 2009. Participants in the Czoski-Murray study wore contact lenses to simulate bilateral visual impairment for a short period of time. In a previous STA, the Committee considered that the participants may have overstated the detrimental impact on health-related quality of life of visual impairment in both eyes because they had little time to adjust to it. Another study, Brown et al 1999, has been used for health related quality of life data in previous appraisals. The Brown study measured health-related quality of life directly from patients with impaired vision in at least 1 eye, so this produced a narrower range of utility values than the study by Czoski-Murray et al. What is the most appropriate source of quality of life data for the economic model?

1 Background: clinical need and practice

1.1 Short-sightedness, or myopia, is a vision problem resulting from excessively long growth of the eye-ball, or a steeply curved cornea. Myopia causes light rays to focus in front of the retina and so close objects are seen clearly whilst distant objects appear blurred. Myopia can be classified as mild, moderate or high, depending on the length of the eye and curvature of the cornea. High myopia (also known as pathological or degenerative myopia) is a chronic condition associated with degenerative changes at the back of the eye. Choroidal neovascularisation (CNV) occurs when the choroid area of the eye produces new blood vessels (neovascularization) which grow up through the damaged layers and leak or bleed into the retina. CNV associated with pathological myopia leads to visual impairment, in particular a loss of central vision. It can also lead to blindness. CNV does not have a direct effect on life expectancy.

1.2 There are approximately 200,000 people with pathological myopia in the UK. The prevalence or incidence of CNV in the UK is not known. However, approximately 30% of the people who develop CNV in one eye will develop it in the other eye within 8 years.

1.3 The aim of current management of CNV is to improve or halt a decline in visual activity. Verteporfin photodynamic therapy (vPDT) is the only treatment with a marketing authorisation for use in subfoveal CNV associated with pathological myopia. Bevacizumab is unlicensed for all eye conditions but it is used for the treatment of CNV associated with pathological myopia. There is no related NICE guidance for the treatment of CNV associated with pathological myopia.

2 The technology

2.1 Ranibizumab (Lucentis, Novartis UK) belongs to a class of drugs that block the action of vascular endothelial growth factor (VEGF-A). By inhibiting the action of VEGF-A, ranibizumab prevents the development of

abnormal blood vessels thereby limiting visual loss and improving vision. Ranibizumab has a UK marketing authorisation for ‘the treatment of visual impairment due to CNV secondary to pathologic myopia’.

2.2 Ranibizumab is administered as a single 0.5 mg intravitreal injection. Each vial of ranibizumab contains 2.3 mg in 0.23 ml; overfilling is considered necessary to achieve an injectable dose of 0.5 mg. The summary of product characteristics states that monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. If monitoring reveals signs of disease activity, e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended.

2.3 Adverse reactions to treatment are mostly limited to the eye. Those commonly reported in clinical trials include vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, sensation of a foreign body in the eye, increased production of tears, blepharitis, dry eye, ocular hyperaemia, itching of the eye and increased intraocular pressure. Nasopharyngitis, arthralgia and headaches are also commonly reported. Contraindications to ranibizumab include known hypersensitivity to the active substance or to any of its excipients, active or suspected ocular or periocular infections, and active severe intraocular inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of ranibizumab 10 mg/ml is £742.17 per 0.23-ml vial (excluding VAT; ‘British national formulary’ [BNF] edition 65). The manufacturer of ranibizumab (Novartis) has agreed a patient access scheme with the Department of Health, revised in the context of technology appraisal guidance 274, which makes ranibizumab available with a discount applied to all invoices. The level of the discount is commercial-in-confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative

burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this technology by NICE is published.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of ranibizumab within its licensed indication for the treatment of CNV associated with pathological myopia.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with visual impairment due to choroidal neovascularisation associated with pathological myopia	People with visual impairment due to choroidal neovascularisation secondary to pathological myopia
Intervention	Ranibizumab	
Comparators	• Verteporfin photodynamic therapy • Bevacizumab	• Verteporfin photodynamic therapy

The manufacturer stated that bevacizumab is not licensed for use in the UK and that the use of bevacizumab is not established practice in the UK. The manufacturer therefore stated that bevacizumab should not be included as a comparator. The ERG state that verteporfin photodynamic therapy (vPDT) is rarely used in clinical practice in the UK because its long term benefits have not been demonstrated. The professional groups also stated that vPDT is rarely used in the UK. The ERG and the patient and professional groups were of the opinion that bevacizumab should have been included as a relevant comparator as it is used in the NHS for the treatment of CNV secondary to pathological myopia.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • Best-corrected visual acuity (the affected eye) • Best-corrected visual acuity (both eyes) • Contrast sensitivity • Adverse effects of treatment • Health-related quality of life	The outcome measures considered are: • Best-corrected visual acuity (the study eye) • Adverse effects of treatment • Health-related quality of life

The manufacturer states that there is insufficient information regarding the effects of vPDT in both eyes to include best-corrected visual acuity (BCVA) as an outcome. The ERG state that BCVA should have been assessed in both eyes.

The manufacturer states that they did not assess contrast sensitivity as the impact of visual impairment on health-related quality of life was likely to be related to the treatment effects on BCVA. The ERG state that the omission of contrast sensitivity as an outcome was acceptable as more relevant outcomes were reported.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness has been expressed in terms of incremental cost per quality-adjusted life year. A lifetime horizon has been chosen to capture all relevant outcomes and costs over the lifetime of patients with choroidal neovascularisation secondary to pathological myopia. Costs have been considered from an NHS and Personal Social Services perspective.

The ERG noted that the scope specifies vPDT and bevacizumab as comparators but that the manufacturer did not consider bevacizumab in their economic evaluation. The ERG highlighted that the health states for the QALY were not described using a standardised and validated instrument and were not drawn from a source that was representative of the public.

3.2 In this appraisal, the manufacturer has positioned ranibizumab for the treatment of people with visual impairment due to choroidal neovascularisation associated with pathological myopia.

4 Clinical-effectiveness evidence

4.1 The manufacturer performed a systematic review for ranibizumab compared with bevacizumab or standard care for CNV (verteporfin photodynamic therapy [vPDT] or laser treatment). Three randomised controlled trials (the Novartis phase III trial [RADIANCE]; Iacono 2012; and Gharbiya 2010) were found that were relevant to the decision problem.

4.2 The Novartis phase III trial compared ranibizumab with vPDT in people with visual impairment due to CNV secondary to pathological myopia. The trial was a randomised, double-blind, multicentre study conducted in 20 countries which compared 2 groups of patients using ranibizumab (n=222) with 1 group using vPDT (n=55). All patients in the 2 ranibizumab groups received initial treatment on day 1 and received retreatment according to predefined criteria. In the ranibizumab disease activity group (n=116), patients were retreated if visual impairment attributable to intra or subretinal fluid, or active leakage secondary to pathological myopia was seen. Treatment was continued in this group until no visual impairment attributable to intra or subretinal fluid, or active leakage secondary to pathological myopia was seen. In the disease stabilisation group (n=106), patients were retreated if there was a loss of BCVA due to disease activity. Treatment was continued until BCVA was stable for 3 consecutive monthly assessments. The vPDT group were given [redacted]. The mean age of the participants was 54 to 57 years across the three groups and 76% of them were female. At baseline, the mean visual acuity was 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

4.3 The primary outcome of the trial was the mean average change in BCVA between baseline and months 1 to 3, measured by ETDRS chart. This was significantly greater in both of the ranibizumab groups compared with the vPDT group. The secondary outcomes included the proportion of patients gaining 10 or more or 15 or more letters, the mean change in BCVA, and changes in central retinal thickness from baseline. There was [redacted] when comparing either of the ranibizumab groups with vPDT in the number of patients who [redacted] and the number of patients who [redacted]. There was no significant difference between either of the ranibizumab groups compared with the vPDT group in mean change in BCVA or in [redacted]. The length of follow up was 12 months for the 2

ranibizumab groups. After 3 months, [redacted] of the patients in the vPDT group received ranibizumab. Therefore, the manufacturer did not compare the results of the vPDT group to the ranibizumab groups after the initial 3 month period. A summary of the efficacy results from the trial is presented in table 1.

Table 1 Summary of primary and secondary outcomes of the Novartis phase III trial from baseline to 3 months

	Ranibizumab (disease activity group) (n=116)		**Ranibizumab (disease stabilisation group) (n=105)**		**vPDT (n=55)**
Outcome	**Mean ± SD or number of patients (%)**	**OR (95% CI) and RR (95% CI) compared with vPDT**	**Mean ± SD or number of patients (%)**	**OR (95% CI) and RR (95% CI) compared with vPDT**	**Mean ± SD or number of patients (%)**
Mean average change in BCVA (letters)	10.6 ± [redacted]**	NR	10.5 ± [redacted]**	NR	2.2 ± [redacted]
Change in BCVA (letters)	12.5 ± [redacted]	NR	12.1 ± [redacted]	NR	1.4 ± [redacted]
Gain of 10 or more letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain of 15 or more letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in CRT (µm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BCVA Best-corrected visual acuity; CI Confidence interval; CRT Central retinal thickness; NR Not reported; OR Odds ratio; RR Relative risk; SD Standard deviation; SE Standard error; vPDT Verteporfin photodynamic therapy

*p<0.01 compared with vPDT group; **p<0.001 compared with vPDT group

4.4 The two other randomised trials (Gharbiya 2010 and Iacono 2012) were single centre trials conducted in Italy that compared ranibizumab with bevacizumab. The Iacono 2012 study was a double-blind clinical trial in people with subfoveal CNV secondary to PM (55 eyes; ranibizumab = 27, bevacizumab = 28) with a follow up period of 18 months. Gharbiya 2010 was an interventional study in people with subfoveal or juxtafoveal CNV

secondary to PM and evidence of leakage from the CNV lesion (32 eyes, ranibizumab = 16, bevacizumab = 16) with a follow up period of 6 months. The results for the ranibizumab arms of each trial are presented in table 2. The manufacturer did not present the data for the bevacizumab arm in either trial.

Table 2 Results for the ranibizumab arms in the Iacono 2012 and Gharbiya 2010 studies

	Mean ± SD or number of patients (%)	
Outcome	**Iacono 2012 (n=27)**	**Gharbiya 2010 (n=16)**
Mean change in BCVA (letters)	9 ± NR	17.31 ± 11.10
Gain of 10 or more letters	NR (NR)	12 (75%)
Gain of 15 or more letters	7 (30%)	9 (56%)
Mean change in retinal thickness (µm)	NR ± NR	-45 ± NR
BCVA Best-corrected visual acuity; NR Not reported; SD Standard deviation		

4.5 The manufacturer identified 6 non-randomised studies that were relevant to the decision problem. All 6 of the studies looked at the use of ranibizumab in patients with CNV secondary to pathological myopia. One study was a multicentre phase II study (REPAIR study) and the other 5 studies were prospective case-series (Calvo-Gonzalez 2011; Lalloum 2010; Ouhadj 2010; Silva 2010; and Vadala 2011). A significant change in BCVA (letters) from baseline to time of assessment was shown in 4 of the 6 studies. The number of participants who gained 15 or more letters at follow-up ranged from 24% to 47% (and up to 60% when including only eyes with improvement). These results from the non-randomised studies are shown in table 3.

Table 3 Summary of results of non-randomised studies of ranibizumab

Study	Number of participants (number of eyes)	Time of assessment or duration of follow up mean ± SD (range)	Change in BCVA (letters), mean ± SD (range)	Gain of 15 letters or more
REPAIR	65 (65)	12 months	13.8 [redacted]	37%
Calvo-Gonzalez 2011	67 (67)[a]	12 months ± NR (range NR)	12.4 ± 13.0* (range NR)	40%
		16 months ± NR (range 6 to 27 months)	12.0 ± 14.6* (range NR)	
Lalloum 2010	32 (32)	Median 17 months (range 7 to 29 months)	9.5 ± NR*** (range NR)	47%
Ouhadj 2010	40 (40)	8 months ± NR (range 3 to 15 months)	15.0 ± NR (range 5 to 45)	NR
Silva 2010	32 (34)	12 months ± NR (range NR)	8.0 ± NR** (range NR)	24%
Vadala 2011	39 (40)	13 months ± 2 (range 12 to 18 months)	Median 14.5[b] (range 5 to 40)	60%[b]

BCVA Best corrected visual acuity; NR Not reported; SD Standard deviation
[a] Results reported here for 59 eyes, [b] For 32 eyes with improvement
*p < 0.05; **p < 0.001; ***p < 0.0001 compared with baseline

4.6 The adverse effects of ranibizumab as reported in the Novartis phase III trial are presented in table 4. There was [redacted] in the number of ocular adverse events in the ranibizumab disease activity group compared with the vPDT group, however there were [redacted] adverse ocular events in the ranibizumab disease stabilisation group compared with the vPDT group. The Iacono 2012 and Gharbiya 2010 studies reported that there were no systemic or significant ocular adverse events in their follow up period (18 months and 6 months respectively). The REPAIR study reported adverse events that occurred in two or more patients. Ocular adverse events occurred in [redacted] patients and non-ocular adverse events in [redacted] patients over 12 months. The Calvo-Gonzalez 2011 study reported that two eyes developed anterior uveitis over a mean length of follow up of 16 months. The other four non-randomised studies (Lalloum 2010; Ouhadj 2010; Silva 2010; Vadala 2011) reported that no systemic or ocular adverse events were observed, with the mean length of follow up ranging from 8 to 17 months.

Table 4 Adverse effects of ranibizumab and verteporfin photodynamic therapy as reported in the Novartis phase III trial

Timeframe	Number of patients (%)		
	Ranibizumab (disease activity group)	**Ranibizumab (disease stabilisation group)**	**vPDT**
Any ocular adverse event			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Baseline to 12 months	44 (37%)	46 (43%)	NR
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular adverse events			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Baseline to 12 months	51 (43%)	48 (45%)	NR
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4.7 Impact on health-related quality of life was measured in the Novartis phase III trial. There was a significant difference in National Eye Institute Visual Functioning Questionnaire 25 item (NEI VFQ-25) composite score for both ranibizumab groups compared with the vPDT group. The statistical significance of the differences between the groups for the EuroQoL-5D (EQ-5D) scores and Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH) scores were not reported. A summary of the health-related quality of life results is presented in table 5.

Table 5 Summary of health-related quality of life results

Outcome	Mean ± SD		
	Ranibizumab (disease activity group)	**Ranibizumab (disease stabilisation group)**	**vPDT**
NEI VFQ-25 composite score			
Change from baseline to 3 months	4.3 ± [redacted]*	5.3 ± [redacted]*	0.3 ± [redacted]
Change from baseline to 6 months	5.1 ± [redacted]	6.3 ± [redacted]	NA
Change from baseline to 12 months	5.1 ± [redacted]	6.6 ± [redacted]	NA
EQ-5D score			
Mean change from baseline to 3 months	[redacted] ± [redacted]	[redacted] ± [redacted]	[redacted] ± [redacted]
Mean change from baseline to 6 months	[redacted] ± [redacted]	[redacted] ± [redacted]	[redacted] ± [redacted]
Mean change from baseline to 12 months	[redacted] ± [redacted]	[redacted] ± [redacted]	[redacted] ± [redacted]
WPAI-GH total score			
Mean reduction from baseline to 3 months	[redacted] ± [redacted]	[redacted] ± [redacted]	[redacted] ± [redacted]
Mean reduction from baseline to 6 months	[redacted]	[redacted]	[redacted]
Mean reduction from baseline to 12 months	[redacted]	[redacted]	[redacted]

EQ-5D 5-dimension EuroQol questionnaire; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; NA Not applicable; NR Not reported; SD Standard deviation; vPDT Verteporfin photodynamic therapy; WPAI-GH Work Productivity and Activity Impairment Questionnaire: General Health

*p<0.05 compared with vPDT group; **p value not reported

Evidence review group comments

4.8 The ERG noted that the manufacturer had excluded bevacizumab as a comparator, despite its use off-label in current clinical practice in the UK. As a result of this, no formal meta-analysis was performed. The ERG found two head to head trials of bevacizumab and ranibizumab (Gharbiya 2010 and Iacono 2012). Neither of these studies showed significant differences in the mean change from baseline in BCVA letters, mean change from baseline in central retinal thickness, or the number of patients gaining 10 or more or 15 or more letters. Follow up was for 6 months in one of the studies (Gharbiya 2010) and 18 months in the other (Iacono 2012).

4.9 The ERG noted that in the Novartis phase III trial the primary endpoint was 3 months, and ERG's clinical opinion was that 12 months should be

the minimum in order to assess longer term efficacy of treatment. The ERG stated that in the VIP trial that compared vPDT with placebo, the statistically significant difference in the primary outcome at 3 months was no longer observed at 24 months, and that the same phenomenon could be observed with ranibizumab. The ERG believe that it is unlikely that a 3 month follow up period would provide adequate information about potential deleterious effects of the anti-VEGF treatment.

4.10 The ERG noted that the manufacturer did not consider atrophy as an adverse event despite the potential effect of anti-VEGF therapies in the development of retinal pigment epithelial atrophy. The ERG stated that VEGF appears to be an essential factor for the maintenance of the retinal pigment epithelium and choriocapillaris, and that blocking the VEGF could have a detrimental effect on these retinal layers, which may lead to visual loss.

5 Comments from other consultees

5.1 The professional groups believe that the use of anti-VEGF therapies is taking precedence over thermal laser and photodynamic therapy. They state that thermal laser coagulation therapy is now almost never used in the UK and many units in the UK no longer provide photodynamic therapy services. They claim that where there is no access to ranibizumab, retinal specialists are likely to recommend bevacizumab on an off label basis, rather than thermal laser or photodynamic therapy. They believe ranibizumab is clinically effective for CNV and the rate of adverse events is low. They do not foresee any implementation issues in terms of facilities or equipment. The professional groups acknowledge that there are risks involved with using anti-VEGF agents, but are in agreement that the risks are outweighed by the potential benefits.

5.2 The patient groups state that people living with the condition are worried about losing their sight and with it their job, ability to drive, and their independence. The patient groups state that the condition tends to affect

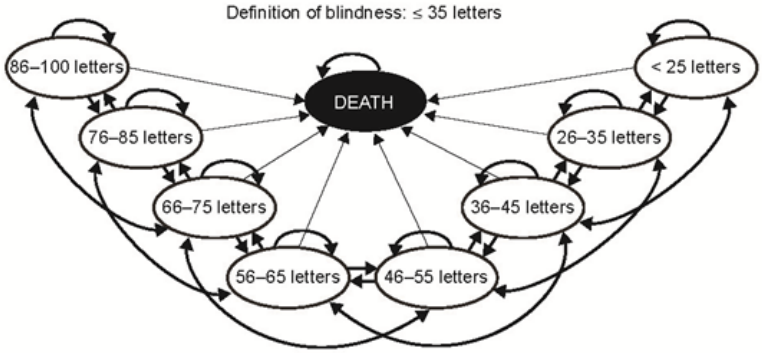
people in their forties and fifties who may have responsibilities such as caring for children and older relatives and paying a mortgage. They state that access to anti-VEGF therapy is available in some parts of the UK but not all, and the inequity in provision can add to patients' distress. Patient groups are in agreement that the most important outcome for patients is not losing their sight, and that ranibizumab offers an effective treatment option.

6 Cost-effectiveness evidence

6.1 The manufacturer identified one existing cost-utility study (Sharma and Bakal 2002) that considered cost-effectiveness of vPDT from the patient and insurer perspective in the United States. The manufacturer judged that the study did not sufficiently address the decision problem and so did not use the study in their health economic analysis.

6.2 The manufacturer developed a cost utility Markov model that evaluated the cost effectiveness of ranibizumab compared with vPDT in people with CNV associated with PM. There were 8 health states in the model defined by the BCVA in the treated eye in addition to the absorbing health state of death, as shown in figure 1. The health states are defined by a 10-letter range in BCVA. The model had three-monthly cycles and a lifetime horizon.

Figure 1 Structure of the manufacturer's health economic model



BCVA	
EDTRS letters	Snellen equivalents
86–100	20/16–20/10
76–85	20/32–20/20
66–75	20/64–20/40
56–65	20/80–20/50
46–55	20/125–20/80
36–45	20/200–20/125
26–35	20/320–20/200
< 25	< 20/320

The arrows shown in this figure apply to the transition probability sensitivity analyses. **For transition probabilities based on current BCVA (base case), patients may move between any two states, so the arrows as depicted on this schematic would extend to all other states.** The arrows have not been completed here for every possible state to maintain legibility.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

6.3 The transition probabilities for the first cycle of the model (baseline to month 3) for both ranibizumab and vPDT were based on the Novartis phase III trial. For the next three cycles (months 4 to 12), the transition probabilities between health states were drawn from the Novartis phase III trial for ranibizumab and from the VIP trial for vPDT. For cycles 5 and onward (1 year onwards), a slow worsening of visual acuity was assumed, based on natural disease progression reported in Yoshida 2002 for the base case and an additional 6 natural history studies for the other transition probabilities. The model accounts for the possibility of the BSE becoming the WSE and vice versa as patients change health states.

6.4 A baseline rate of bilateral involvement (i.e. both eyes being affected by CNV) of 15% was drawn from two published studies (Cohen 1996 and Hampton 1983) and the model assumes there are no incidences of CNV secondary to PM subsequent to the baseline. Based on expert opinion, the manufacturer's estimate a recurrence in 6% of patients each year after the first two years of modelling.

6.5 The health-related quality of life data collected in the Novartis phase III trial was not deemed by the manufacturer to be relevant to the economic model. Base case utility values for the better-seeing eye (BSE) were taken from a published study performed in the UK general population

where BCVA health states were simulated with contact lenses that created the effects of age-related macular degeneration (Czoski-Murray 2009). There was no direct clinical trial data presented by the manufacturer for health related quality of life. Base case utility values for the worse-seeing eye (WSE) were calculated from the values for the BSE, with the assumption that the maximum gain in the WSE was 0.1 (see table 6).

Table 6 Base case utilities

	Base case utilities	
Health state	**Czoski-Murray 2009**	**Assumption based on Czoski-Murray 2009**
	Better-seeing eye	**Worse-seeing eye**
BCVA 86 to 100 letters	0.850	0.850
BCVA 76 to 85 letters	0.758	0.836
BCVA 66 to 75 letters	0.685	0.821
BCVA 56 to 65 letters	0.611	0.807
BCVA 46 to 55 letters	0.537	0.793
BCVA 36 to 45 letters	0.464	0.779
BCVA 26 to 35 letters	0.390	0.764
BCVA <25 letters	0.353	0.750
Death	0.000	0.000
BCVA Best-corrected visual acuity		

6.6 Disutilites were defined as adverse events that occurred in more than 5 patients and that were suspected to be related to the study drug or ocular injection in the Novartis phase III trial (for ranibizumab) or VIP trial (for vPDT). The durations of disutilities were taken from published sources or were assumptions (see table 7).

Table 7 Summary of disutilities, duration and cost

Adverse event	Incidence		Disutility	Duration (months)
	Ranibizumab	vPDT		
Conjunctival haemorrhage	8.5%	0%	0.02[a]	1[b]
Intraocular pressure increased	4.2%	0%	0.01[c]	0.03[c]
Visual disturbance	0%	[redacted]	0.00[b]	0[b]
Injection site adverse event	0%	[redacted]	0.1336[e]	0.2696[e]

vPDT Verteporfin photodynamic therapy

Source of information: [a]Brändle et al. 2007; [b]Assumption; [c]Vaahtoranta-Lehtonen 2007; [d]Sum of costs of beta-blockers, prostaglandins, CA inhibitors, combination, and brimonidine; [e]Brown 2005

6.7 Total costs for treatment were calculated from the unit costs for ranibizumab or vPDT, administration, and a monitoring visit, multiplied by the number of treatment and monitoring visits required. The direct drug costs in the model were [redacted] for ranibizumab, including the PAS, and £850.00 for vPDT. Administration costs for ranibizumab were £168.53 and for vPDT were £174.89. Monitoring visit costs were £174.89 for either treatment. The number of treatment and monitoring visits required is shown in table 8. A cost of £17,325 associated with blindness was applied for the first year when the BSE was declared blind (BCVA of 35 letters or less). The cost for year 2 onwards was £17,245.

Table 8 Summary of visits required to treat or monitor

Treatment	Year 1 visits		Year 2 visits		Year 3 visits	
	To treat	To monitor	To treat	To monitor	To treat	To monitor
Ranibizumab	3.5[a]	8.5[c]	1[c]	4[c]	0[d]	0[d]
vPDT	3.4[b]	4[c]	1.7[b]	4[c]	0[d]	0[d]

vPDT Verteporfin photodynamic therapy

[a]Bandello et al., 2013 (publication from the Novartis phase III study); [b]VIP study group 2001; [c]Assumption based on posology for vPDT; [d]Based on information from an advisory board

6.8 The manufacturer base case deterministic cost effectiveness results showed that ranibizumab dominated vPDT resulting in more QALYs (13.18 compared with 12.75) and lower costs (£9694 compared with £12,455). The manufacturer also presented base case probabilistic results which showed that ranibizumab dominates vPDT (see table 9).

Table 9 Base case cost effectiveness using deterministic and probabilistic values

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY (ICER)
Deterministic results					
Ranibizumab	£9694	13.18	-£2751	0.43	Dominant
vPDT	£12,445	12.75	--	--	--
Probabilistic results					
Ranibizumab	£9422	12.53	-£2691	0.42	Dominant
vPDT	£12,113	12.11	--	--	--
ICER Incremental cost-effectiveness ratio; QALYs Quality-adjusted life-years; vPDT Verteporfin photodynamic therapy					

6.9 The manufacturer conducted one-way sensitivity analyses using a net monetary benefit approach because ranibizumab dominated vPDT in the base case analysis. The sensitivity analysis showed that the cost effectiveness of ranibizumab was most sensitive to changes in the unit cost of ranibizumab and vPDT, the number of ranibizumab injections in the first and second year, the starting age of the patient cohort, the discount rate for benefits and the maximum utility gain in the WSE. The results of the manufacturer's sensitivity analysis show that ranibizumab remains dominant up to a unit cost of £783 (range £0 to £3750) and when up to 12 injections are needed in either year 1 or year 2 (range 0 to 12, with vPDT given 3.4 times per year). Scenario analyses show that ranibizumab remains dominant when other methods for calculating transition probabilities and other sources of natural history are used, and when the maximum gain in utility for the WSE is 0.2 or 0.3. The sensitivity analysis shows that the probability of cost effectiveness for ranibizumab is 99.3% at a willingness-to-pay threshold of £0, and 100% at a threshold of £20,000 or £30,000.

6.10 The manufacturer conducted three scenario analyses. The first scenario analysis involved calculating the transition probabilities from patient-level data using three different methods. The base case method used probabilities that were dependent on the current BCVA level and assumed

the patient could move from any health state to any other health state in each cycle. The second method used probabilities that were dependent on the patients' current BCVA level for the top two health states only, so that a patient could only gain or lose up to 2 health states in each cycle. The third method used a constant probability across all BCVA levels, regardless of the patient's current BCVA level, and assumed that patients could only gain or lose up to 2 health states each cycle. The second scenario analysis involved using different sources for calculating transition probabilities beyond year 1. The third scenario analysis involved using different values for the maximum utility gains for the WSE. Ranibizumab continued to dominate vPDT in all of the scenario analyses.

Evidence review group comments

6.11 The ERG considered that the manufacturer's model was broadly reasonable. The ERG, however, identified some areas of uncertainty in the manufacturer's model:

- Bevacizumab was not included as a comparator
- The model accounts for the possibility of the BSE becoming the WSE, or vice versa, as patients change health states. The method used seems to underestimate the net QALY gains and cost of blindness offsets that may arise from the more effective treatment
- There is some discrepancy between the transition probability matrices and the patient level data supplied at clarification
- A large number of health state probabilities were populated by relatively few patients
- The use of multipliers in the probabilistic modelling is unusual
- The vPDT data were drawn from a population with a higher proportion of patients with subfoveal involvement, which is associated with a worse prognosis
- EQ-5D data from the Novartis phase III trial were not used

- Data from Czoski-Murray 2009 were used for health-related quality of life. Previous STAs have used health-related quality of life data from Czoski-Murray 2009 and Brown 1999
- The number of ranibizumab injections needed in years 2 and 3 may have been underestimated
- The annual costs of blindness and depression may have been overestimated
- There are alternative interpretations of the study that provided the blindness mortality multipliers which affect the QALY gain and associated costs
- The average BCVA gains modelled at the end of year 1 appear to continue indefinitely. This seems to be optimistic
- The method used to calculate the cyclical worsening from natural studies is unclear for most of the studies
- There is an error in the calculation of the quarterly rate of worsening used for extrapolating beyond the first year. This has been acknowledged in the manufacturer's response to ERG clarification queries.

6.12 The ERG amended the manufacturer's model as shown in table 10.

Table 10 ERG's amendments to the manufacturer's model

Variable	Manufacturer's model	ERG's model
Source of utility values	Czoski-Murray 2009	Czoski-Murray 2009 or Brown 1999
Dose of ranibizumab in year 2	1	1.7
Cost of blindness	£17,326 in year 1 and £17,245 each year after	£7510 in year 1 and £7429 each year after
Blindness mortality multiplier (when the BSE is 35 letters or less)	1.54	1.48
BSE Better-seeing eye; vPDT Verteporfin photodynamic therapy		

The ERG also corrected the calculation of natural history quarterly worsening and the impact of adverse events on quality of life as specified in the manufacturer's response to clarification comments. The other

weaknesses identified in the model could not be amended by the ERG. The ERG's revised base case shows a reduction in net savings, net patient benefits and net health benefit, however, ranibizumab continues to dominate vPDT (see table 11).

Table 11 ERG's revised base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY (ICER)
Using Brown 1999 utility values					
Ranibizumab	£10,055	14.514	-£2474	0.344	Dominant
vPDT	£12,529	14.170	--	--	--
Using Czoski-Murray 2009 utility values					
Ranibizumab	£10,055	13.105	-£2474	0.266	Dominant
vPDT	£12,529	12.838	--	--	--
ICER Incremental cost-effectiveness ratio; QALYs Quality-adjusted life-years; vPDT Verteporfin photodynamic therapy					

The ERG undertook sensitivity analyses around the assumed duration of benefit, the proportion of eyes that are BSEs, and including all of the natural history studies. The use of ranibizumab resulted in a decrease in cost and increase in QALYs compared with vPDT in all but one of the sensitivity analyses. The exception was using a combination of 5 year duration of benefit, natural decline based all natural history studies, and Czoski-Murray 2009 utility values, which resulted in a small decrease in QALYs.

7 Equality issues

7.1 Comments from patient groups identified that the condition is more likely to affect people of working age. They also highlighted that there is currently inequity in access to ranibizumab treatment. No additional equality issues were identified by the manufacturer or ERG.

8 Innovation

8.1 The manufacturer states that ranibizumab is the first licensed therapy to specifically target the pathogenesis of CNV secondary to pathological myopia. The manufacturer states that the current standard treatment (vPDT) stabilises but does not improve visual acuity. The manufacturer states that ranibizumab has a greater positive effect on patients' health-related quality of life compared with the current treatment option of vPDT. The QALY does not capture the benefits that arise from not losing contrast sensitivity and the visual field, which include maintaining depth perception and reading speed. The manufacturer states that the use of ranibizumab constitutes a step change in the management of visual impairment due to CNV secondary to pathological myopia.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Aflibercept solution for injection for treating wet age-related macular degeneration. NICE technology appraisal guidance TA294 (2013).
- Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. NICE technology appraisal guidance TA283 (2013).
- Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy. NICE technology appraisal guidance TA271 (2013).
- Ranibizumab for the treatment of diabetic macular oedema (rapid review of TA237). NICE technology appraisal guidance TA274 (2013).
- Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance TA155 (2008, reissued 2012).
- Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion. NICE technology appraisal guidance TA229 (2011).
- Guidance on the use of photodynamic therapy for age-related macular degeneration. NICE technology appraisal guidance TA68 (2003).

Appendix B: Clinical efficacy section of the draft European public assessment report

[This has been requested]