NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Aflibercept solution for injection for the treatment of wet age-related macular degeneration

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

Clinical Effectiveness

- Does the Committee consider it appropriate for the manufacturer to exclude bevacizumab for intravitreal injection and photodynamic therapy as comparator treatments, despite both being listed as comparators in the scope for this appraisal?

- Both the manufacturer and the ERG noted their concerns about the validity of the network meta-analyses and indirect comparisons for outcomes at 12 and 24 months because of the presence of heterogeneity. What is the Committee's view on the strength of the evidence from these analyses on the effectiveness of aflibercept compared with ranibizumab in a 'treatment as needed' regimen?

- Are the discontinuation rates reported for patients treated with aflibercept in the VIEW 1 and 2 studies likely to be reflected in UK clinical practice?

Cost effectiveness

- The manufacturer assumed that the untreated second eye has no wet age-related macular degeneration or visual impairment at the start of the economic model and that there was no incidence of second-eye involvement in years 1 and 2 of the model. Does the Committee consider these assumptions to be appropriate or does it agree with the ERG that the manufacturer's economic model in its current form is a 'one-eye model' that should be limited to considering the cost effectiveness of aflibercept as unilateral treatment for wet age-related macular degeneration?

- Does the Committee agree with the ERG's alternative approach to modelling the cost effectiveness of aflibercept as unilateral treatment for wet age-related macular degeneration, which involved separate analyses depending on whether it was a worse-seeing eye model or better-seeing eye model?

- Does the Committee consider that the frequency of aflibercept (n=7) and ranibizumab (n=8) injections in the first year of the manufacturer's economic model is correct?

- Are the costs of administration visits and optical coherence tomography used in the manufacturer's model reasonable or does the Committee agree with the lower costs proposed by the ERG, which resulted in smaller differences in treatment and monitoring costs between aflibercept and ranibizumab?

- In the economic model, the manufacturer applied relative risks of maintaining and gaining visual acuity for ranibizumab compared with aflibercept for year 1 compared with baseline and for year 2 compared with year 1. Does the Committee agree with the manufacturer's interpretation that the 24 month analyses from the indirect comparison provide relative risks relating to the 12 to 24 months period, or does the Committee support the ERG's view that the relative risks relate to the baseline to 24 months period?

- The manufacturer considers aflibercept solution for injection to be an innovative treatment for wet age-related macular degeneration. Does the Committee agree?

1 Background: clinical need and practice

1.1 The macula is the central part of the retina responsible for colour vision and perception of fine detail. Age-related macular degeneration refers to the deterioration in the cells of the retinal pigment layer at the macula area, which can lead to severe visual impairment in the affected eye. Age-related macular degeneration usually affects both eyes but the speed in which it progresses can vary from eye to eye.

1.2 Age-related macular degeneration is a common cause of vision loss in people aged over 50 years and is associated with the loss of central vision and visual distortion. There are two main types of age-related macular degeneration, wet (neovascular) and dry (non-neovascular). Wet age-related macular degeneration is characterised by pathological choroidal neovascularisation which involves the formation of immature blood vessels that grow between the retinal pigment epithelial cells and the photoreceptor

cells in the centre of the retina. These new blood vessels are fragile and more likely to haemorrhage, which causes scarring of the macula leading to vision impairment. Choroidal neovascularisation can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. Choroidal neovascularisation can also be described in terms of its location in relation to the fovea, which is a small depression in the macula that provides the clearest vision: subfoveal (extending behind the middle of the fovea); juxtafoveal (in the remainder of the fovea but not the middle) and extrafoveal (in the macula excluding the fovea). Wet age-related macular degeneration usually progresses much more quickly than dry age-related macular degeneration, making serious changes to central vision in a short period of time.

1.3 People with wet age-related macular degeneration retain peripheral vision but lose the ability to see detail, often leaving them unable to read, see faces, watch television, drive or carry out many other everyday tasks. Severe visual loss is associated with chronic morbidity, increased depression, diminished quality of life due to high levels of emotional distress and increased risk of falls and mortality.

1.4 There are an estimated 26,000 new cases of wet age-related macular degeneration in the UK each year. Risk factors for the development of age-related macular degeneration include increasing age, sex (it is more common in women), cigarette smoking (smokers having a 3.6 times greater risk of developing age-related macular degeneration compared with people who have never smoked), and exposure to high levels of UV light.

1.5 The aim of current management of age-related macular degeneration is to improve or halt the decline in visual acuity. Treatment needs to be given rapidly before new blood vessels cause excess damage to the macula, leading to scarring and permanent sight loss. NICE technology Appraisal No. 68 recommends the use of photodynamic therapy (laser activation of verteporfin which causes cell death in new blood vessels) in individuals with a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation and a best-corrected visual acuity 6/60 or better. NICE Technology Appraisal No. 155 recommends the use of intravitreal ranibizumab for the treatment of wet age-related macular degeneration if all of the following apply: the best possible visual acuity after correction with glasses or contact lenses is between 6/12 and 6/96; there is no permanent structural damage to the central fovea; the area affected by the condition is no larger than 12 times the size of the area inside the eye where the optic nerve connects to the retina; there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes).

1.6 The Royal College of Ophthalmologists has issued a statement that supports the use of intravitreal bevacizumab rather than ranibizumab for the treatment of wet age-related macular degeneration if it is in the patient's best interest, the ophthalmologist sources the bevacizumab from a reputable pharmacy and the patient gives informed consent (December, 2011). Current patient management also involves social support, visual rehabilitation and the provision of aids to help with low vision.

2 The technology

2.1 Aflibercept solution for injection (Eylea, Bayer Pharma; hereafter referred to as aflibercept) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and the placental growth factor (PlGF). VEGF-Trap prevents these factors from stimulating the growth of fragility and permeable new blood vessels associated with wet age-related macular degeneration. Aflibercept has a UK marketing authorisation 'for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)'.

2.2 The summary of product characteristics states that aflibercept treatment should be given monthly for 3 consecutive 2 mg doses, followed by 1 injection every 2 months, with each 100 microlitre vial containing 4 mg of aflibercept. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. There is no requirement for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician.

2.3 The summary of product characteristics lists the following most common adverse reactions for aflibercept solution for intravitreal injection: conjunctivial haemorrhage, eye pain, vitreous detachment, cataract, vitreous floaters and increased intraocular pressure. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The list price of aflibercept 40 mg/ml solution for injection is £816 per vial (excluding VAT; 'British national formulary' [BNF] edition

52). The manufacturer has agreed a patient access scheme with the Department of Health which involves a confidential [redacted] discount applied to the list price of aflibercept. The acquisition cost of aflibercept 40 mg/ml solution for injection within the patient access scheme is [redacted] per vial. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

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 aflibercept, within its licensed indication, for the first-line treatment of wet age-related macular degeneration.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with wet age-related macular degeneration	Adults with neovascular (wet) age-related macular degeneration
Intervention	Aflibercept solution for injection	Aflibercept solution for injection
Comparators	• Ranibizumab • Bevacizumab • Photodynamic therapy	• Ranibizumab

The manufacturer stated that, bevacizumab is not licensed for use in wet age-related macular degeneration and should therefore not be included as a comparator when a licensed alternative treatment (ranibizumab) is available. The manufacturer also highlighted concerns about the safety of bevacizumab when prepared for intravitreal use including an increased risk of infection. The ERG commented that, although a recently published study (CATT, 2012) showed a higher proportion of adverse events in patients treated with bevacizumab compared with ranibizumab, the study was not adequately

powered to detect reliable clinical differences in adverse events. The ERG suggested that the safety of bevacizumab as an intravitreal injection should be investigated further and that this should be balanced against the comparable clinical effectiveness with ranibizumab and the large difference in the cost per single dose. Therefore, the ERG considered that bevacizumab should have been included as a comparator treatment.

The manufacturer stated that photodynamic therapy (PDT) should not be included as a comparator because, although published guidance in 2003 (NICE technology appraisal 68) recommended PDT for a subgroup of patients with classic with no occult subfoveal choroidal neovascularisation and a best-corrected visual acuity of 6/60 or better, current practice has subsequently changed for this subgroup and newer treatments have superseded PDT for the treatment of wet age-related macular degeneration. The ERG commented that PDT is often recommended as a treatment option in patients with idiopathic polypoidal choroidal vasculopathy who may not respond to anti-VEGF treatment. Therefore, the ERG considered that PDT should also have been included as a comparator treatment.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life

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 economic evaluation should be based on an appropriate time horizon over which the main costs and benefits of treatment are likely to differ from the standard comparator. Costs will be considered from an NHS and Personal Social Services perspective.	Incremental cost per quality-adjusted life year. (25 year) lifetime horizon Costs will be considered from an NHS and Personal Social Services perspective

3.2 In this appraisal, the manufacturer has positioned aflibercept for the treatment of adults with wet age-related macular degeneration.

4 Clinical-effectiveness evidence

4.1 The manufacturer performed a systematic literature review of the evidence on the clinical effectiveness of aflibercept. The review identified 2 studies that directly compared aflibercept with ranibizumab in people with wet age-related macular degeneration – VIEW 1 (n=1,217) and VIEW 2 (n=1,240). Both studies were multicentre (VIEW 1: 142 centres in USA and Canada; VIEW 2: 172 centres in 26 countries), active-controlled, double-masked, randomised trials that compared aflibercept with ranibizumab. Both studies were identical in design (except for location) so that data could be pooled. Only one eye per patient was enrolled in both studies. If a patient needed treatment in the second eye during the study, the second eye was allowed to receive any approved treatment although it was not considered to be an additional study eye. In both studies patients were randomised on

a 1:1:1:1 basis to receive either (i) aflibercept 2 mg every 8 weeks after 3 initial monthly loading doses (2 mg Q8); (ii) aflibercept 2 mg every 4 weeks; (iii) aflibercept 0.5 mg every 4 weeks; (iv) or ranibizumab 0.5 mg every 4 weeks (0.5 mg Q4). The manufacturer stated that both studies were designed primarily to test whether aflibercept at its recommended dose (2 mg Q8) was non-inferior to ranibizumab 0.5 mg Q4. Therefore, the results reported here are limited to these treatment arms of both studies. Both studies had 2 phases, including a primary phase (from randomisation to week 48) during which patients received treatment according to randomisation arm, with patients in the aflibercept 2 mg Q8 arm receiving sham injections when no active treatment was due. In the follow-up extension phase (up to 92 weeks), patients in all 4 treatment arms continued to be evaluated every 4 weeks and remained in their allocated treatment groups. The total duration of both studies was 96 weeks consisting of up to 92 weeks of treatment plus a screening period and a 4-week safety follow-up period.

4.2 For both studies, the manufacturer defined 3 populations for analysis. The full analysis set (FAS) included all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment. The per protocol set (PPS) included all patients in the FAS who received at least 9 injections of study drug or sham and attended at least 9 scheduled visits during the first 52 weeks, except for those who were excluded because of major protocol violations. The safety analysis set (SAF) included all patients who received any study drug. The manufacturer stated that the PPS was used for primary analysis (statistical evaluation of non-inferiority). A patient who withdrew from the study before week 36 because of treatment failure was

considered a non-responder. The last observation carried forward (LOCF) approach was used to impute missing data except for baseline values. Patients withdrawing before week 36 were not included in the primary analysis but were included in the secondary analysis (in FAS).

4.3 The baseline demographics and disease characteristics were similar between the aflibercept (2 mg Q8) and ranibizumab treatment arms in the VIEW 1 and 2 studies. In VIEW 1, the mean age was 78 years, 41-43% of patients were male, and 95-97% of patients were white. In VIEW 2, the mean age was 73-74 years, 42-43% of patients were male, and 71-73% of patients were white. The total mean baseline best-corrected visual acuity score (defined by Early Treatment Diabetic Retinopathy Study [ETDRS] scale) ranged between 54-56 letters in VIEW 1 and 52-54 letters in VIEW 2. In both studies, the distribution of occult, minimally classic and predominantly classic lesion types in the study eye was similar across both treatment arms.

4.4 The primary outcome of VIEW 1 and 2 was the proportion of patients who maintained vision at week 52, defined as losing fewer than 15 letters on the ETDRS scale compared to baseline. This outcome was also measured at week 96. The manufacturer stated that aflibercept demonstrated non-inferiority to ranibizumab at weeks 52 and 96 because the upper limits of the confidence intervals for the differences in proportions were consistently below a pre-specified boundary of 10%. Aflibercept also met a pre-specified 7% non-inferiority margin compared with ranibizumab in a pooled analysis of both studies at week 52. The manufacturer also evaluated the primary outcome for pre-planned subgroup analyses in both studies by age, gender, race, renal function,

hepatic impairment, baseline visual acuity, lesion size and type. The manufacturer stated that the results for all subgroups in both studies and in pooled analyses were consistent with the results in the whole study populations. However, the results of these subgroup analyses were not presented by the manufacturer. A summary of the proportion of patients who maintained vision at weeks 52 and 96 in VIEW 1 and 2 is presented in table 1.

Table 1. Summary of results for the proportion of patients who maintained vision after 52 and 96 weeks in VIEW 1 and 2

	Ranibizumab 0.5mg Q4		**Aflibercept 2mg Q8**		**Difference (95% CI)**
	n/N	**%**	**n/N**	**%**	
Week 52 (PPS including LOCF)					
VIEW 1	254/269	94.4	252/265	95.1	-0.7 (-4.5, 3.1)
VIEW 2	254/269	94.4	258/270	95.6	-1.13 (-4.81, 2.55)
Pooled	508/538	94.4	510/535	95.3	-0.9 (-3.5, 1.7)
Week 96 (FAS including LOCF)					
VIEW 1	273/304	89.8	275/301	91.4	-1.6 (-6.2, 3.1)
VIEW 2	272/391	93.5	286/306	93.5	0.0 (-4.0, 4.0)
Pooled	545/595	91.6	561/607	92.4	-0.8 (-3.8, 2.3)
FAS, Full Analysis set; LOCF, Last observation carried forward; PPS, Per Protocol set; 95% CI, 95% Confidence interval					

4.5 Secondary outcomes in VIEW 1 and 2 included changes from baseline to week 52 for: best-corrected visual acuity as measured by ETDRS letter score, proportion of patients gaining at least 15 letters, and choroidal neovascularisation (CNV) area. For the outcome of best-corrected visual acuity, mean ETDRS letter scores increased in both treatment arms in VIEW 1 and 2 by approximately 8-10 letters at week 52. No statistically significant differences in change in best-corrected visual acuity from baseline to week 52 were reported between aflibercept and ranibizumab in

VIEW 1 (mean difference: 0.26 letters, 95% confidence interval [CI] -1.97 to 2.49) or VIEW 2 (mean difference: -0.90 letters, 95% CI -3.06 to 1.26). [redacted] No statistically significant differences in the proportion of patients who gained at least 15 ETDRS letters were reported between aflibercept and ranibizumab at week 52 in VIEW 1 (30.6% versus 30.9%, p=0.93) or VIEW 2 (31.4% versus 34.0%, p=0.49). [redacted] In VIEW 1, the ranibizumab arm experienced a statistically significantly greater mean reduction in CNV area at week 52 compared with the aflibercept arm (-4.2 mm^2 versus -3.4 mm^2, p=0.017). No statistically significant differences were reported between ranibizumab and aflibercept 2 mg Q8 at week 52 in VIEW 2 (-4.16 mm^2 versus -5.16 mm^2, p=0.073).

4.6 VIEW 1 and 2 both measured vision-related quality of life using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), which includes 25 questions designed to measure the effect of visual impairment on daily functioning and quality of life. Improvements in the mean NEI VFQ-25 total score from baseline to week 52 were similar in both the aflibercept and the ranibizumab treatment arms in VIEW 1 (5.1 points versus 4.9 points, p=0.5579) and VIEW 2 (4.9 points versus 6.3 points, p=0.072). [redacted] The VIEW 2 study also measured changes in health-related quality of life using the EuroQol-5D (EQ-5D) questionnaire which were incorporated in the manufacturer's cost-effectiveness analysis.

4.7 The manufacturer did not present a formal meta-analysis of the VIEW 1 and 2 studies on the basis that both studies were similarly designed so that their data could be pooled directly. The manufacturer commented that, although the VIEW 1 and 2 studies used a fixed dosing regimen for ranibizumab (0.5 mg Q4), in clinical practice a 'treat-to-target' approach is used which involves monthly ranibizumab treatment until the patient's visual acuity is stable for 3 consecutive months, with re-treatment in a similar way upon loss of visual acuity (with a minimum of 2 injections). Therefore, the manufacturer conducted a systematic literature review and mixed treatment comparison (network meta-analysis) to compare aflibercept 2 mg Q8 with ranibizumab 0.5 mg in a 'treatment as needed' regimen (also referred to as 'pro re nata' [PRN]).

4.8 The manufacturer produced 3 networks at 6, 12 and 24 months. Because no data were available for aflibercept at 6 months, only networks for outcomes at 12 and 24 months were considered further by the manufacturer. The manufacturer assumed that 52 and 96 week data from VIEW 1 and 2 corresponded with outcomes at 12 and 24 months respectively. Results were presented for 3 outcomes: maintained vision (defined as the proportion of patients losing ≤ 15 ETDRS letters), improved vision (defined as the proportion of patients gaining > 15 ETDRS letters) and mean change from baseline in best-corrected visual acuity. The network meta-analysis of outcomes at 12 months incorporated up to 10 studies, depending on the outcome, and included the VIEW 1 and 2 studies. The manufacturer did not present a network meta-analysis of outcomes at 24 months because VIEW 1 and 2 both allowed treatment switching after 12 months from a fixed dosing regimen of aflibercept (2 mg Q8) to a

PRN regimen (2 mg Q8). Therefore, two step indirect comparisons, based on the Bucher method, were used to compare aflibercept 2 mg Q8 fixed/PRN with ranibizumab 0.5 mg PRN. The indirect comparisons included data from 3 studies: VIEW 1 and 2 and CATT, a 2-year study comparing ranibizumab 0.5 mg with bevacizumab for the treatment of patients with wet age-related macular degeneration (CATT Research Group, 2012). The CATT study presented data for ranibizumab as an identical switch trial and as fixed dose or PRN only. Both sets of data from the CATT study were analysed for the indirect comparison.

4.9 The manufacturer presented separate network meta-analyses, using both frequentist methods, based on traditional statistical methods applied in making comparisons, and Bayesian methods, which combine the probability of the data as a function of the parameters with prior beliefs about possible values of those parameters. Both analyses showed no statistically significant differences between aflibercept 2 mg Q8 and ranibizumab 0.5 mg PRN for the 3 outcomes at 12 months. For the outcome of mean change in best-corrected visual acuity, the manufacturer repeated the analyses after excluding one study (DETAIL) because patients in the study responded differently to treatment compared to other patient study groups. However, exclusion of this study did not significantly affect the results of the analyses. The results of the manufacturer's network meta-analyses for outcomes at 12 months are presented in table 2.

Table 2. Results of 12-month Network Meta-Analysis: Aflibercept 2 mg Q8 versus Ranibizumb 0.5 mg PRN

	No. Trials	**Frequentist Method: Mean (95% CI)**	**Bayesian Method: Mean (95% CrI)**
Maintained vision	4 (VIEW 1, VIEW 2, CATT, HARBOR)	OR = 1.44 (0.68 to 3.09)	OR = 1.51 (0.42 to 5.94) RR = 1.01 (0.98 to 1.12)
BCVA mean change from baseline	10 (VIEW 1, VIEW 2, CATT, HARBOR, DETAIL, MARINA, PIER, EXCITE, EXTEND, MOON)	MD = 0.83 (-1.57 to 3.23) MD = 1.35 (-1.08 to 3.77)*	MD = -2.87 (-10.02 to 4.30) MD = 1.15 (-3.92 to 6.09)*
Improved Vision	4 (VIEW 1, VIEW 2, CATT, HARBOR)	OR = 1.29 (0.91 to 1.83)	OR = 1.28 (0.45 to 3.68) RR = 1.15 (0.71 to 2.40)
BCVA, Best-corrected visual acuity; CrI, Credible Interval; MD, mean difference; OR, Odds-Ratio; RR, Relative Risk * Results of analyses after excluding DETAIL study			

4.10 The manufacturer's indirect comparison also showed no statistically significant differences between aflibercept 2 mg Q8 fixed/PRN and ranibizumab 0.5 mg PRN for the 3 outcomes at 24 months (when switch data from the 3 studies were used). The results of the manufacturer's indirect comparison for outcomes at 24 months are presented in table 3.

Table 3. Results of 24-month Indirect Comparison: Aflibercept 2 mg Q8 fixed/PRN versus ranibizumab fixed/PRN (using switch data only)

	No. Trials	**Effect Size (95% CI)**
Maintained vision	3 (VIEW 1, VIEW 2, CATT)	OR = 0.91 (0.36 to 2.34) RR = 0.99 (0.93 to 1.07)
BCVA mean change from baseline	3 (VIEW 1, VIEW 2, CATT)	MD = 0.31 (-4.33 to 3.71)
Improved Vision	3 (VIEW 1, VIEW 2, CATT)	OR = 0.84 (0.61 to 1.28) RR = 0.88 (0.50 to 1.42)

4.11 The manufacturer highlighted concerns about the validity of the network meta-analyses and indirect comparisons because of the heterogeneity between the included studies. On the basis of a quality assessment checklist, the manufacturer found that 3 of the included studies had a high risk of bias. The manufacturer also noted that several of the studies had different baseline characteristics in terms of ETDRS letter score, PRN retreatment criteria, proportion of males, central retinal thickness and numbers of injections. The manufacturer commented that sensitivity analyses were performed with regard to the heterogeneity but that the results were unchanged. However, no further details on these sensitivity analyses were presented by the manufacturer.

4.12 The manufacturer stated that the safety and tolerability of aflibercept compared with ranibizumab for up to 96 weeks was included as a secondary objective in the VIEW 1 and 2 studies. On the basis of the safety analysis dataset, no clinically meaningful differences were reported between aflibercept and ranibizumab for treatment-emergent adverse events with similar incidences of reported events between treatment arms. The most common treatment-emergent adverse events (reported in at least 5% of patients treated with aflibercept in VIEW 1 and 2) were: conjunctivial haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%).

4.13 The ERG considered that the clinical-effectiveness evidence from the VIEW 1 and 2 studies was of good quality without any obvious sources of bias. The ERG noted that the primary outcome (maintained vision at week 52) in both studies was analysed using a non-inferiority approach and that the margin of non-inferiority was chosen as a difference of 10% in the proportion of patients losing less than 15 ETDRS letters. The ERG's clinical specialists suggested that a non-inferiority margin based on a mean change in best-corrected visual acuity, which was used in the CATT study, would have been more appropriate. When the ERG applied a non-inferiority margin of 5 letters for mean change in best-corrected visual acuity between aflibercept and ranibizumab in a pooled analysis of VIEW 1 and 2, non-inferiority was established (mean difference -1.95, 95% CI -4.10 to 0.20). Therefore, despite its initial concerns, the ERG considered that the manufacturer's choice of a non-inferiority margin of 10% was appropriate.

4.14 The ERG noted that the manufacturer used the last observation carried forward approach to impute missing data for the primary outcome of the proportion of patients who maintained vision at week 52 in VIEW 1 and 2. The ERG considered that this approach may have introduced bias because it can artificially stabilise disease, which may be inappropriate for a progressive disease such as wet age-related macular degeneration. Following clarification, the manufacturer provided the observed results at week 52 for the outcome of maintained vision from the per protocol and full analysis data sets, which were not significantly different from the results based on the last observation carried forward approach. The ERG also ran the network meta-analysis for the outcome of maintained vision at 12 months using observed data from VIEW 1 and 2 and found that the results did not differ significantly from the original results obtained using the last observation carried forward approach. Therefore, the ERG was satisfied that the use of last observation carried forward did not substantially impact the results for the primary outcome at week 52 in VIEW 1 and 2.

4.15 The ERG agreed with the manufacturer that there were concerns regarding the validity of the network meta-analyses and indirect comparison because of heterogeneity between the included studies. The ERG noted that the manufacturer had conducted sensitivity analyses with regard to heterogeneity, but commented it was not clear what these sensitivity analyses were. The ERG also noted that the network meta-analysis for the outcome of mean change from baseline in best-corrected visual acuity at 12 months excluded a treatment arm from one of the studies included in the analysis (ranibizumab fixed dose 0.3 mg arm in the DETAIL study). The ERG was concerned about the validity of

the results as a result of this omission and therefore repeated the analysis including this treatment arm. The ERG found that, although this did not significantly alter the results in terms of the mean difference in change in best-corrected visual acuity between treatment arms, the results of the network analyses and indirect comparison should be interpreted with caution.

5 Comments from other consultees

5.1 Clinical specialists stated that wet age-related macular degeneration is currently treated with ranibizumab in line with NICE technology appraisal guidance 155. However, they noted that it is necessary for ranibizumab to be administered to patients every 4 weeks and that very few NHS trusts were able to manage these patients at such regular intervals, resulting in delays to treatment to every 6-8 weeks. Audits on ranibizumab therapy from several departments in the UK suggest that the current treatment regimen is inadequate and so the visual outcomes are inferior to results reported in clinical trials. Therefore, the clinical specialists noted that one advantage of aflibercept is that it is administered every 8 weeks with no additional monitoring or resources in terms of staff, education or training, thus imposing less burden on NHS capacity, and is clinically non-inferior to ranibizumab which is administered every 4 weeks. It was also highlighted that the first year of treatment for wet age-related macular degeneration is crucial and, because aflibercept is administered at a fixed dose in the first year of treatment, patients will receive the optimal level of treatment for their condition during this period rather than physician guided treatment as needed option for ranibizumab.

5.2 Patient experts commented that wet age-related macular degeneration can develop very quickly and lead to permanent

visual impairment in a short period of time. Therefore, it is essential that patients receive rapid access to diagnosis and treatment for their condition and aflibercept provides an additional treatment option which is particularly important for those who do not respond to ranibizumab. They also highlighted the significant negative impact that visual impairment has on the physical and emotional well-being of people with wet age-related macular degeneration. Patient experts noted that, because aflibercept is associated with less frequent treatment and monitoring visits compared with ranibizumab, it will also reduce the burden on patients and their carers in terms of time off work and travel costs. They noted that, although the intravitreal injections caused some initial pain and anxiety for patients, these side effects were tolerable. Patient experts also noted that a reduction in the number of injections would reduce the risk of endophthalmitis and the need for antibiotics.

6 Cost-effectiveness evidence

6.1 The economic evidence provided by the manufacturer included a literature review, which identified one published cost-effectiveness analysis of aflibercept in US patients with wet age-related macular degeneration, and a de novo cost–utility analysis. The manufacturer developed a Markov state-transition cohort model simulating cohorts of people with wet age-related macular degeneration receiving aflibercept 2 mg Q8 or ranibizumab 0.5 mg PRN. The model assumed a cycle length of 1 month based on the level of monitoring associated with ranibizumab treatment, and used a lifetime horizon (25 years based on a starting age of 74 years). An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

6.2 The economic model included a total of 30 health states defined by a combination of different levels of visual acuity in both eyes (the treated eye and the second eye) in addition to the absorbing health state of death. For each health state, visual acuity in the treated eye or second eye was defined according to 5 possible levels of the ETDRS scale, ranging from no visual impairment (ETDRS > 80 letters) to blindness (ETDRS < 36 letters) with 3 intermediate levels defined by a range of 15 ETDRS letters. In each model cycle, people were assumed to have the median visual acuity of each ETDRS range and moved to the median value of either the adjacent state or the state two levels higher or lower, based on the number of letters gained or lost. For each health state, the patient could either be on or off active treatment. A summary of the 30 health states defined according to level of visual acuity is presented in table 4.

Table 4. Health states defined by visual acuity in manufacturer's model

Visual acuity in second eye	**Visual acuity in treated eye**				
	No visual impairment (> 80 letters)	**Mild visual impairment (66-80 letters)**	**Moderate visual impairment (51-66 letters)**	**Severe visual impairment (36-50 letters)**	**Blind (< 36 letters)**
No visual impairment and no wet AMD	1	2	3	4	5
No visual impairment	6	7	8	9	10
Mild visual impairment	11	12	13	14	15
Moderate visual impairment	16	17	18	19	20
Severe visual impairment	21	22	23	24	25

Blind	26	27	28	29	30

6.3 The economic model included a 5-year treatment period on the basis of clinical opinion which suggested that patients are likely to continue treatment beyond 24 months. For the first 2 years, clinical effectiveness data at baseline, 52 and 96 weeks from the last observation carried forward population in the VIEW 2 study were used to estimate the visual acuity of people receiving aflibercept. The probabilities of gaining and losing visual acuity in year 1 were applied to the VIEW 2 patient distribution at baseline and the probabilities of gaining and losing visual acuity in year 2 were applied to the modelled year 1 distribution. The visual acuity of people receiving ranibizumab for the first 2 years of the model was estimated from the relative risks of gaining and maintaining vision with ranibizumab treatment taken from the manufacturer's indirect comparison of aflibercept 2 mg Q8 with ranibizumab 0.5 mg PRN. During this period, people who were defined as being in the blind health state received treatment with ranibizumab or aflibercept but this did not continue in years 3 to 5 on the basis of clinical opinion which suggested that the blind eye is unlikely to benefit from treatment. Simple linear interpolation was used to populate the monthly model cycles for year 1 (cycles 1-12) and year 2 (cycles 13-24). Treatment discontinuation rates were assumed to be identical between both treatment groups and were based on an average of the discontinuation rates reported in the VIEW 2 and CATT studies.

6.4 For years 3 to 5 in the model, it was assumed that people on active treatment would remain in the same health state that they were in after 2 years. Because no significant differences in clinical

effectiveness were identified in the indirect comparison of aflibercept with ranibizumab, identical assumptions were made for both treatment groups during this period. In the absence of available trial data, clinical opinion was used to estimate rates of treatment discontinuation in years 3 to 5, which were also assumed to be identical between treatment groups. From year 6 it was assumed that people in both treatment groups discontinued active treatment and started best supportive care.

6.5 The manufacturer assumed that clinical effectiveness in the treated eye was independent of effectiveness in the second eye. Clinical effectiveness data for the second eye while on treatment was calculated using the same methodology applied to the treated eye. The manufacturer assumed that wet age-related macular degeneration involvement in both eyes was 0% at the start of the model and that people developed wet age-related macular degeneration in the second eye from year 3. The manufacturer also assumed that all people in the model who developed wet age-related macular degeneration in the second eye from year 3 were treated. On the basis of a meta-analysis by Wong et al. (2008) of patients with wet age-related macular degeneration receiving no active treatment, the manufacturer estimated a 0.65% monthly probability of developing wet age-related macular degeneration in the second eye. For people who were not receiving active treatment, clinical effectiveness data from Wong et al. were used to estimate the monthly probability of losing either 15 or 30 letters with the remaining people maintaining stable visual acuity.

6.6 The manufacturer stated that there is limited evidence of a relationship between wet age-related macular degeneration and

an increased risk of mortality and that, on the basis of data from the VIEW 1 and 2 studies, it is unlikely that there is any difference in mortality between aflibercept and ranibizumab. Therefore, age-specific all-cause mortality rates from UK life tables were used for both treatment groups. For people in the blind health state, an excess risk of mortality was taken from a UK study of older patients with visual impairment by Thiagarajan et al. (2005). A summary of the key clinical effectiveness parameters used in the model is presented in table 5.

Table 5. Summary of clinical effectiveness parameters used in manufacturer's economic model.

Variable	**Value (Distribution)**			**Source**
Relative risks aflibercept versus ranibizumab – Year 1 compared to baseline				
Maintaining vision	1.02 (95% CI 0.98 to 1.06)			Manufacturer's indirect comparison (ITC)
Gaining 15-29 letters	1.19 (95% CI 0.93 to 1.51)			Manufacturer's ITC
Gaining ≥ 30 letters	1.19 (95% CI 0.93 to 1.51)			Manufacturer's ITC
Relative risks aflibercept versus ranibizumab – Year 2 compared to Year 1				
Maintaining vision	0.99 (95% CI 0.93 to 1.07)			Manufacturer's ITC
Gaining 15-29 letters	0.88 (95% CI 0.61 to 1.28)			Manufacturer's ITC
Gaining ≥ 30 letters	0.88 (95% CI 0.61 to 1.28)			Manufacturer's ITC
Annual probability of discontinuation – Both treatment groups				
Year 1	0.027 (SE 0.005)			VIEW 2 and CATT
Year 2	0.035 (SE 0.007)			VIEW 2 and CATT
Years 3-5	0.187 (SE 0.037)			Clinical opinion
Annual probability of change in visual acuity in Year 1 – Best supportive care				
Losing 15 letters	0.065 (SE 0.013)			Wong et al.
Losing 30 letters	0.172 (SE 0.034)			Wong et al.
No change	0.763 (residual)			Wong et al.
Visual acuity distribution (First eye)				
Health State	**Baseline**	**Year 1 Aflibercept**	**Year 2 Aflibercept**	

No visual impairment	[redacted]	15.6%	16.7%	VIEW 2
Mild visual impairment	[redacted]	26.6%	23.9%	VIEW 2
Moderate visual impairment	[redacted]	27.9%	25.7%	VIEW 2
Severe visual impairment	[redacted]	18.7%	19.0%	VIEW 2
Blind	[redacted]	10.4%	13.2%	VIEW 2
Dead	0%	0.8%	1.6%	Thiagarajan et al.

6.7 To estimate the health-related quality of life associated with each health state corresponding to visual acuity in both eyes, EQ-5D data from VIEW 2 were transformed to utility values using the UK population tariff. A pooled data set of all trial arms at baseline, 52 weeks and 96 weeks was used by the manufacturer. The manufacturer adjusted the utility values for 4 of the health states in the model to maintain the assumption that utility values decrease monotonically with worsening visual acuity. This was achieved by taking the average of the utility values above and below the anomalous value. Utility values were not adjusted for age in the model. A summary of the adjusted utility values is presented in table 6. The manufacturer stated that, because of the low rates of adverse events observed in the VIEW 1 and 2 trials and the small differences observed between the aflibercept and ranibizumab treatment groups, the impact of adverse events on HRQoL was not included in the base case analysis. However, in a scenario analysis, the manufacturer included the loss in utility associated with adverse ocular events taken from 2 separate studies identified in a systematic literature review (Brown et al. 2007; Gower et al. 2010). These included retinal haemorrhage (-0.300), vitreous haemorrhage (-0.305), endophthalmitis (-0.300), cataract (-0.142) and retinal detachment (-0.27).

Table 6. Summary of adjusted utility values used in economic model

	VA in treated eye				
VA in Fellow Eye	**No VI**	**Mild VI**	**Moderate VI**	**Severe VI**	**Blind**
No VI	[redacted]				
Mild VI	[redacted]	[redacted]			
Moderate VI	[redacted]	[redacted]	[redacted]		
Severe VI	[redacted]	[redacted]	[redacted]	[redacted]	
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VA = Visual Acuity; VI = Visual Impairment
NB: Values in bold text have been adjusted to impose monotonicity

6.8 The manufacturer included the costs of drug treatment, including drug acquisition, administration and monitoring costs. Under the terms of the patient access scheme approved by the Department of Health, the cost of aflibercept was [redacted] per injection. Ranibizumab is administered as a single intravitreal injection of 0.5 mg per vial The list price of ranibizumab is £742.17 per vial (excluding VAT; 'British national formulary' [BNF] edition 65). The manufacturer of ranibizumab has also previously agreed a patient access scheme with the Department of Health. In its submission, the manufacturer of aflibercept therefore presented a range of scenario analyses which applied discounts to the list price of ranibizumab ranging from 10% to 50%, in increments of 5%.

6.9 The resource use and unit costs associated with treatment and monitoring visits were based on Hospital episode statistics

(2010/11) and NHS reference costs (2011/12). The manufacturer assumed that in year 1, people treated with aflibercept had their treatment administration and monitoring at the same visit (one stop model) and 50% of people treated with ranibizumab followed a one-stop model and 50% had separate visits for treatment and monitoring (two stop model). In years 2 to 5, the manufacturer assumed that 50% of people in both treatment groups followed a one-stop model and 50% followed a two-stop model. The manufacturer assumed that treatment with both aflibercept and ranibizumab occurred as a weighted average of a day case visit (55%) and outpatient visit (45%), resulting in a total cost of £257.45 per treatment visit. It was assumed that people in both treatment groups would need one fluoroscein angiography (£117) before starting treatment.

6.10 The manufacturer assumed that people receiving aflibercept had 7 injections in the first year and 4 injections in the second year based on the treatment frequency recommended in the summary of product characteristics and the VIEW 2 study. It was assumed that people receiving ranibizumab had 8 injections in the first year and 6 injections in the second year based on NICE technology appraisal guidance 155 and the revised summary of product characteristics. Based on clinical expert opinion, the manufacturer assumed that people in both treatment groups had 4 injections in years 3 to 5. The manufacturer also assumed that separate patient monitoring visits included the cost of an ophthalmologist outpatient visit (£80) and an optical coherence tomography (£117), resulting in a total cost of £197 per monitoring visit. The frequency of monitoring visits in the first 2 years of the model was also based on the summary of product characteristics for both treatments. The frequency of monitoring visits in years 3 to 5 was

based on clinical expert opinion. A summary of the frequency of treatment and monitoring visits in both treatment groups is presented in table 7.

Table 7. Number of treatment and monitoring visits in aflibercept and ranibizumab treatment groups in manufacturer's model

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept					
Treatment visits	7	4	4	4	4
Monitoring visits (two stop model)	7*	6	7	7	7
Monitoring visits (one stop model)	0	2	3	3	3
Ranibizumab					
Treatment visits	8	6	4	4	4
Monitoring visits (two stop model)	12	12	7	7	7
Monitoring visits (one stop model)	4	6	3	3	3
*NB: all patients in the aflibercept group follow one-stop model for treatment administration in year 1					

6.11 The manufacturer estimated the costs associated with blindness for people who were defined as being blind in both eyes (ETDRS < 36 letters). The manufacturer applied cost data taken from a published UK costing study of blindness in people with age-related macular degeneration (Meads and Hyde 2003). This study estimated the costs associated with a range of items including low-vision aids, rehabilitation, residential care, district nursing, community care and the cost of treating complications including depression and falls. After adjusting for inflation, the total estimated annual cost of blindness was £585. Because of the low incidence of adverse events reported in the VIEW 1 and 2

studies, the manufacturer did not apply the costs of adverse events in the base-case analysis.

6.12 The manufacturer's base-case deterministic cost-effectiveness results (including the patient access scheme for aflibercept but not for ranibizumab) showed that aflibercept dominated ranibizumab, resulting in lower costs ([redacted] compared with £28,615) and higher QALYs (7.767 compared with 7.759). When the manufacturer applied a discount to the list price of ranibizumab, ranging from 10 to 50%, aflibercept continued to dominate ranibizumab (see table 8).

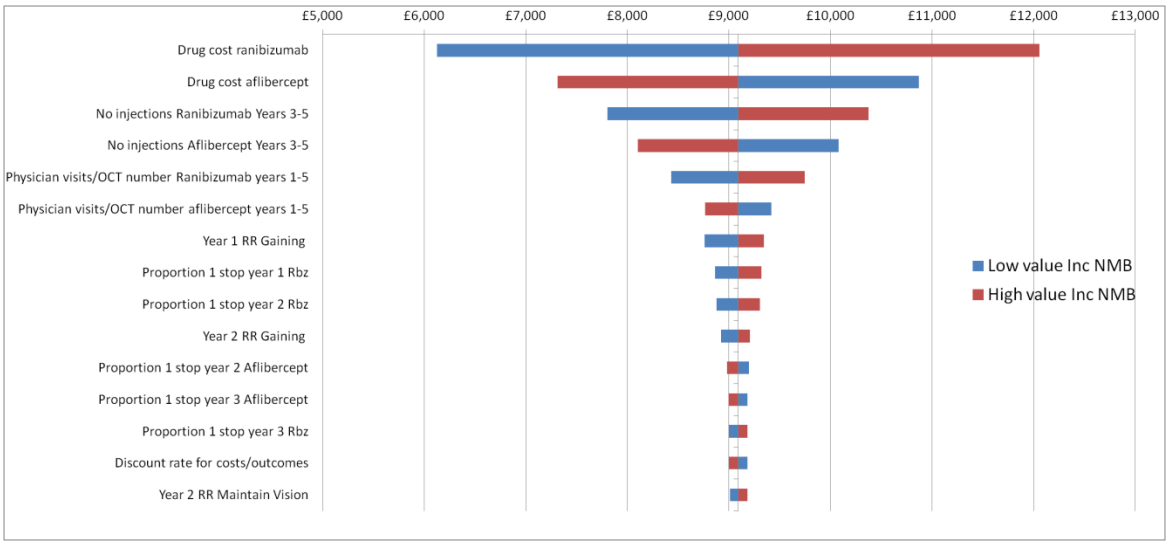
Table 8. Manufacturer's deterministic results (including the patient access scheme discount for aflibercept and a range of discounts to the ranibizumab list price)

Technologies	Total costs (£)	Total Life years gained (LYG)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	10.575	7.77				
Ranibizumab (0% discount)	£28,615	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (10% discount)	£27,132	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (15% discount)	£26,391	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (20% discount)	£25,650	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (25% discount)	£24,908	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (30% discount)	£24,167	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (35% discount)	£23,425	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (40% discount)	£22,684	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (45% discount)	£21,942	10.574	7.76	[redacted]	-0.001	-0.010	Dominated
Ranibizumab (50% discount)	£21,201	10.574	7.76	[redacted]	-0.001	-0.010	Dominated

6.13 The manufacturer performed one-way sensitivity analysis using a net monetary benefit approach because aflibercept dominated ranibizumab in the base-case analysis[1]. The sensitivity analyses included the discounted price for aflibercept agreed under the patient access scheme but did not explore parameter uncertainty based on a discounted price for ranibizumab. The results of the one-way sensitivity analyses indicated that the cost effectiveness of aflibercept was most sensitive to the drug acquisition costs, frequency of injections and monitoring visits, proportion of people in one-stop and two-stop models, discount rates and the relative risk of gaining or losing visual acuity with ranibizumab treatment (see figure 1). The manufacturer stated that, in all sensitivity analyses, aflibercept continued to dominate ranibizumab. Results of the manufacturer's probabilistic sensitivity analysis showed that, at a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained, aflibercept had the highest probability (100%) of being cost effective.

[1] Net Marginal Benefit (NMB) = (£20000*Incremental QALYs) – Incremental Costs

Figure 1. Tornado diagram of one-way sensitivity analysis (including patient access scheme discount for aflibercept; no patient access scheme discount for ranibizumab)



NB: Horizontal axis represents net monetary benefit for aflibercept compared with ranibizumab

6.14 The manufacturer also conducted a number of scenario analyses, which included the discounted price for aflibercept but not for ranibizumab. Two scenarios involved varying the frequency of injections and monitoring: applying the average number of injections reported in years 1 and 2 of the VIEW 2 and CATT trials for aflibercept and ranibizumab respectively, and applying monthly monitoring visits for ranibizumab and bi-monthly monitoring visits for aflibercept in years 3 to 5. One scenario involved applying the same clinical effectiveness data for both treatments so that the same proportions of people gaining or losing visual acuity were applied in both treatment groups. One scenario applied alternative utility values from a study by Czoski-Murray et al. (2009) in which members of the general public valued levels of visual impairment that were simulated by custom-made contact lenses, using the time trade-off method. One scenario modelled the impact of adverse ocular events in the

ranibizumab treatment group, which included retinal haemorrhage, vitreous haemorrhage, endophthalmitis, cataract and retinal detachment taken from a separate trial of ranibizumab in patients with wet age-related macular degeneration (Boyer et al., 2009). Another scenario applied clinical effectiveness estimates equivalent to best-supportive care, taken from Wong et al., in years 3-5 for both treatment groups. For all scenario analyses, aflibercept either continued to dominate ranibizumab or resulted in net cost savings (when the same proportions of people gaining or losing visual acuity were applied in both treatment groups).

6.15 The ERG noted that clinical effectiveness data for the aflibercept treatment group were derived from the VIEW 2 study rather than pooled data from VIEW 1 and 2. The ERG also noted that the proportion of patients treated with aflibercept who gained or lost visual acuity at 52 weeks and 96 weeks was broadly similar between VIEW 1 and 2 and that there was no suggestion of bias arising from the choice of VIEW 2 data rather than pooled clinical effectiveness data. However, the ERG highlighted that there were discrepancies between the clinical effectiveness data from VIEW 2 and the modelled population in terms of the proportion of people who gained or maintained visual acuity at week 52. The ERG commented that it was unclear what clinical effectiveness data were used for the aflibercept group in the model.

6.16 The ERG noted that patients treated with aflibercept in VIEW 1 and 2 received an average of 7.5 and 7.7 injections in the first year of both studies. The ERG also noted from the summary of product characteristics for aflibercept that the dosing schedule suggests that patients who remain on treatment would need 8

injections in year 1. Therefore, the ERG considered that it may have been more reasonable for the manufacturer to model 8 injections of aflibercept in year 1. The ERG also considered that, on the basis of the average number of injections of ranibizumab in a treatment as needed dosing regimen in studies included in the manufacturer's systematic review, the number of ranibizumab injections in year 1 of the model should have been 7 rather than 8.

6.17 The ERG noted that the manufacturer reported relative risks of maintaining and gaining visual acuity from its network meta-analysis and indirect comparison between baseline and 12 months and between 12 months and 24 months. However, the ERG considered that the results of the manufacturer's systematic review and indirect comparison at 24 months were the relative risks of gaining or maintaining visual acuity between baseline and 24 months. The ERG also noted that applying the 24-month relative risks to the probability of gaining or maintaining visual acuity between 12 months and 24 months, resulted in more people in the aflibercept treatment group gaining or maintaining visual acuity compared with ranibizumab at 24 months. However, the ERG considered that, because the estimated relative risks of gaining and maintaining visual acuity for aflibercept compared with ranibizumab from baseline to 24 months were less than 1, fewer people in the aflibercept treatment group should have gained or maintained visual acuity compared with ranibizumab at 24 months.

6.18 The ERG considered that the manufacturer's approach to modelling second-eye involvement was incorrect. The ERG noted that the probabilities of gaining or maintaining visual acuity with

aflibercept or ranibizumab during the first 2 years of treatment were not applied to the second eye and that there was no incidence of second-eye involvement in years 1 and 2 of the model. The ERG also noted that, although the baseline prevalence of wet age-related macular degeneration in the second eye was 19% in the pooled VIEW 1 and 2 population, the manufacturer had assumed that people in both treatment groups had no visual impairment or wet age-related macular degeneration in their second eye at the start of the model. Furthermore, the ERG considered that the model did not allow for sensible consideration of the timing of second-eye involvement because the effect of treatment on visual acuity in the second eye and the costs of treating any second-eye involvement were limited to years 3 to 5. Therefore, the ERG concluded that the manufacturer's economic model in its current form is a 'one-eye model' that should be limited to considering the cost effectiveness of aflibercept as unilateral treatment for wet age-related macular degeneration.

6.19 Because the ERG concluded that the manufacturer's model may be limited to being a one-eye model, it suggested that further consideration should be given as to whether people received treatment in their better-seeing eye or their worse-seeing eye and the resultant impact on health-related quality of life. The ERG considered that the manufacturer's assumption of zero second-eye involvement in years 1 and 2 resulted in the model being a worse-seeing eye model, with the additional assumption of the second eye having no visual impairment. On the basis of the manufacturer's EQ-5D utility values from VIEW 2, the ERG suggested that the utility values would range from [redacted] to [redacted] for the 5 health states defined by visual acuity in a worse-seeing eye

model. For a better-seeing eye model, the ERG suggested that utility values should be taken from a study by Brown (1999) that measured vision-related utility values using the time trade-off method in 325 people from the USA with impaired vision (Snellen scale 20/40) in at least 1 eye. The ERG noted from the Brown study that, among people who had good vision in their better-seeing eye, the worse-seeing eye contributed little to health-related quality of life. The utility values taken from the Brown study ranged from 0.920 to 0.621 for the 5 health states defined by visual acuity in the manufacturer's model, a range that the ERG noted was similar to the range of utility values from the VIEW 1 study (▇▇▇ to ▇▇▇) under the assumption of the worse-seeing eye being blind.

6.20 The ERG considered that it was unclear why all patients in the aflibercept group followed a one-stop monitoring model and 50% of patients in the ranibizumab group followed one-stop and 50% followed a two-stop model in the first year of the economic model. The ERG also considered that the manufacturer's estimated cost per treatment visit of £257, which was based on a weighted average of outpatient and day case visits from 2010/11 Hospital Episode Statistics (HES) data, may have been too high. On the basis of 2011/12 HES data, the ERG estimated a lower weighted average cost of £129.46 per treatment visit. The ERG also noted that, in the appraisal of ranibizumab for treating diabetic macular oedema (NICE technology appraisal guidance 237), the manufacturer estimated a total cost of £143 per treatment visit. The ERG also considered that the manufacturer's estimated cost of £117.26 for an optical coherence tomography (based on a fluoroscein angiography) may have been too high and that a lower cost of £51.27 (based on a 20-minute ultrasound scan) may

have been more appropriate. The ERG also noted that the manufacturer's estimate of the annual costs of blindness was implemented as a monthly cost in the model.

6.21 The ERG conducted exploratory analyses, which involved the following modifications to the manufacturer's model:

- second-eye involvement after year 1 and 2 was set to zero to reflect the ERG's view that the submitted modelling of second eye involvement is untenable
- 8 injections in year 1 were assumed for both treatments groups
- treatment visit costs were reduced to £129.46 and optical coherence tomography costs to £51.27
- 50% of people in both treatment groups were monitored according to the one stop model in year 1
- utility values for a better-seeing eye model (see section 6.18) were drawn from the Brown study, ranging from 0.920 to 0.621; utility values for a worse-seeing eye model were consistent with those used in the manufacturer's submission ([redacted] to [redacted])

6.22 The ERG applied the changes outlined in section 6.21 in two scenario analyses for the worse-seeing eye model and two scenario analyses for the better-seeing eye model. The first scenario for each model adopted the manufacturer's interpretation that its indirect comparison of aflibercept with ranibizumab at 24 months provided relative risks of maintaining and gaining visual acuity from 12 to 24 months. In this first scenario, the ERG retained the proportions of people maintaining and gaining visual acuity in the manufacturer's original model. The second scenario for each model adopted the ERG's interpretation that the manufacturer's indirect comparison at 24 months provided relative

risks of gaining and maintaining visual acuity from baseline to 24 months. In this second scenario, the ERG retained the baseline distribution of visual acuity from the manufacturer's original model.

6.23 The ERG's first scenario analysis for the worse-seeing eye model resulted in aflibercept dominating ranibizumab (incremental costs [redacted]; incremental QALYs 0.007). When the ERG applied a discount to the list price of ranibizumab, ranging from 10 to 50%, aflibercept either dominated ranibizumab (discount 10-45%) or resulted in an ICER of [redacted] per QALY gained (discount 50%). The ERG's first scenario analysis for the better-seeing eye model resulted in aflibercept dominating ranibizumab (incremental costs [redacted]; incremental QALYs 0.045). When the ERG applied a discount to the list price of ranibizumab, ranging from 10 to 50%, aflibercept either dominated ranibizumab (discount 10-45%) or resulted in an ICER of [redacted] per QALY gained (discount 50%).

6.24 The ERG's second scenario analysis for the worse-seeing eye model resulted in an ICER for ranibizumab compared with aflibercept of [redacted] per QALY gained (incremental costs [redacted]; incremental QALYs 0.004). When the ERG applied a discount to the list price of ranibizumab, ranging from 10 to 45%, the ICERs for the comparison of ranibizumab with aflibercept ranged from [redacted] per QALY gained to [redacted] per QALY gained. When the ERG applied a 50% discount to the list price of ranibizumab, aflibercept was dominated by ranibizumab. The ERG's second scenario analysis for the better-seeing eye model resulted in an ICER for ranibizumab compared with aflibercept of [redacted] per QALY gained (incremental costs [redacted]; incremental QALYs 0.027). When the ERG applied a discount to the list price of ranibizumab, ranging from 10 to 45%, the ICERs for

ranibizumab compared with aflibercept ranged from [redacted] per QALY gained to [redacted] per QALY gained. When the ERG applied a 50% discount to the list price of ranibizumab, aflibercept was dominated by ranibizumab.

7 Equalities issues

7.1 During scoping consultation, one consultee noted that older people, women and smokers are at higher risk of developing wet age-related macular degeneration. However, at the scoping workshop it was agreed that, while these were risk factors for developing wet age-related macular degeneration, they did not constitute an equality consideration for this appraisal.

8 Innovation

8.1 The manufacturer stated that aflibercept should be considered innovative because it has a different mode of action to other VEGF inhibitors, addressing a wider range of growth factors including the placental growth factor. It also highlighted that aflibercept may result in a step-change in the management of wet age-related macular degeneration because it is associated with less frequent treatment and monitoring compared with other treatments. The manufacturer commented that the resultant impact on ophthalmology services was unlikely to be captured in the QALY calculation.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance 155 (2008). Available from www.nice.org.uk/guidance/TA155
- The clinical effectiveness and cost effectiveness of photodynamic therapy for age-related macular degeneration. NICE technology appraisal guidance 168 (2003). Available from www.nice.org.uk/guidance/TA68
- Macular translocation with 360° retinotomy for wet age related macular degeneration. NICE interventional procedure guidance 340 (2010). Available from www.nice.org.uk/guidance/IPG340
- Limited macular translocation for wet age-related macular degeneration. NICE interventional procedure guidance 339 (2010). Available from www.nice.org.uk/guidance/IPG339
- Implantation of miniature lens systems for advanced age-related macular degeneration. NICE interventional procedure guidance 272 (2008). Available from www.nice.org.uk/guidance/IPG272
- Transpupilary thermotherapy for age-related macular degeneration. NICE interventional procedure guidance 58 (2004). Available from www.nice.org.uk/guidance/IPG58
- Radiotherapy for age-related macular degeneration. NICE interventional procedure guidance 49 (2004). Available from www.nice.org.uk/guidance/IPG49
- Macular translocation for age-related macular degeneration. NICE interventional procedure guidance 48 (2004). Available from www.nice.org.uk/guidance/IPG48

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Epiretinal brachytherapy for wet age related macular degeneration. NICE interventional procedure guidance. Available from www.nice.org.uk/guidance/IPGXXX