

# Aflibercept solution for injection for treating wet age-related macular degeneration

Technology appraisal guidance  
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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Guidance

- 1.1 Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:
- it is used in accordance with the recommendations for ranibizumab in [NICE technology appraisal guidance 155](#) (re-issued in May 2012) **and**
  - the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.
- 1.2 People currently receiving aflibercept solution for injection whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

## 2 The technology

- 2.1 Aflibercept solution for injection (Eylea, Bayer Pharma) 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. Aflibercept solution for injection prevents these factors from stimulating the growth of the fragile and permeable new blood vessels associated with wet age-related macular degeneration. Aflibercept solution for injection 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 the recommended dose for aflibercept is 2 mg and that treatment should be given monthly for 3 consecutive doses, followed by 1 injection every 2 months. Each 100-microlitre vial contains 4 mg of aflibercept. Aflibercept solution for injection must only be administered by a qualified doctor experienced in administering intravitreal injections. The summary of product characteristics also states that there is no need 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 doctor.
- 2.3 The summary of product characteristics lists the following most common adverse reactions for aflibercept solution for injection: conjunctival 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 100-microlitre vial (excluding VAT; 'British national formulary' [BNF] edition 52). The manufacturer of aflibercept solution for injection has agreed a patient access scheme with the Department of Health. This involves a confidential discount applied to the list price of aflibercept solution for injection. The level of the discount is commercial in confidence (see [section 5.3](#)). 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 NICE technology appraisal guidance is published.

## 3 The manufacturer's submission

The Appraisal Committee ([section 8](#)) considered evidence submitted by the manufacturer of aflibercept solution for injection and a review of this submission by the Evidence Review Group (ERG; [section 9](#)).

### Clinical effectiveness

3.1 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=1217) and VIEW 2 (n=1240). Both studies were multicentre (VIEW 1: 154 centres in USA and Canada; VIEW 2: 172 centres in 26 countries, including the UK), active-controlled, double-blind, 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 included 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 included in the study. 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, (ii) aflibercept 2 mg every 4 weeks, (iii) aflibercept 0.5 mg every 4 weeks, or (iv) ranibizumab 0.5 mg every 4 weeks. The manufacturer stated that both studies were designed primarily to test whether aflibercept at its recommended dose (2 mg every 8 weeks) was non-inferior to ranibizumab (0.5 mg every 4 weeks). Therefore, the results reported here are limited to the treatment arms of both studies. The manufacturer stated that non-inferiority margins and definitions were established in discussion with the US Food and Drugs Administration, European Medicines Agency and other regulatory agencies to be consistent with key trials of ranibizumab, including the MARINA study (2006), for treating wet age-related macular degeneration. 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 every 8 weeks 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.

- 3.2 For both studies, the manufacturer defined 3 populations for analysis. The full analysis set included all randomised patients who received any study drug and had a baseline and at least 1 post-baseline assessment. The per protocol set included all patients in the full analysis set 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 included all patients who received any study drug. The manufacturer stated that the per protocol set 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 approach was used to calculate 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 the full analysis set).
- 3.3 The baseline demographics and disease characteristics were similar between the aflibercept 2 mg every 8 weeks and ranibizumab treatment arms in the VIEW 1 and 2 studies. In VIEW 1, the mean age was 78 years, 41% of patients were male, and 97% of patients were white. In VIEW 2, the mean age was 73–75 years, 45% of patients were male, and 73% of patients were white. The total mean baseline best-corrected visual acuity score (defined by Early Treatment Diabetic Retinopathy Study [ETDRS] scale) ranged from 54 to 56 letters in VIEW 1 and from 52 to 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.
- 3.4 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 with baseline. This outcome was also

measured at week 96. In a pooled analysis of both studies, the proportion of patients treated with aflibercept who maintained vision at week 52 was 95.3% compared with 94.4% of patients treated with ranibizumab (difference -0.9%, 95% confidence interval [CI] -3.5 to 1.7). At week 96, the proportion of patients treated with aflibercept who maintained vision was 92.4% compared with 91.6% of patients treated with ranibizumab (difference -0.8%, 95% CI -3.8 to 2.3). The manufacturer stated that aflibercept showed 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 the pre-specified boundary of 10%. The manufacturer also evaluated the primary outcome for pre-planned subgroup analyses in both studies by age, sex, 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.

- 3.5 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 area. For the outcome of best-corrected visual acuity at week 52, mean ETDRS letter scores increased by approximately 7–11 letters in both treatment arms in VIEW 1 and by approximately 8–10 letters in VIEW 2. No statistically significant differences in change in best-corrected visual acuity from baseline to week 52 were reported between aflibercept and ranibizumab in a pooled analysis of both studies (mean difference -0.32 letters, 95% CI -1.87 to 1.23). In VIEW 1 and 2, improvements in visual acuity observed at week 52 were largely maintained at week 96 in both treatment arms. No statistically significant differences in the proportion of patients who gained at least 15 ETDRS letters were reported between aflibercept and ranibizumab treatment arms at week 52 in a pooled analysis of both studies (30.97% and 32.44% respectively, p-value not reported). Similar results were reported at week 96. In VIEW 1, the ranibizumab arm had a statistically significantly greater mean reduction in choroidal neovascularisation area at week 52 than the aflibercept arm (-4.2 mm<sup>2</sup> and -3.4 mm<sup>2</sup>

respectively,  $p=0.017$ ). No statistically significant differences in choroidal neovascularisation area at week 52 were reported between ranibizumab and aflibercept 2 mg every 8 weeks in VIEW 2 ( $-4.16 \text{ mm}^2$  and  $-5.16 \text{ mm}^2$  respectively,  $p=0.073$ ). Similar results were also reported at week 96 in both studies.

- 3.6 Vision-related quality of life was measured in VIEW 1 and 2 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 a pooled analysis of both studies (5.0 points and 5.6 points respectively,  $p$ -value not reported). These improvements in vision-related quality of life were maintained at week 96 in both treatment arms. The VIEW 2 study also measured changes in health-related quality of life using the EQ-5D questionnaire, which were incorporated in the manufacturer's cost-effectiveness analysis.
- 3.7 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 every 4 weeks), in clinical practice a 'treatment as needed' 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 every 8 weeks with ranibizumab 0.5 mg in a 'treatment as needed' regimen.
- 3.8 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-week 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 or fewer ETDRS letters), improved vision (defined as the proportion of patients gaining more than 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. For the outcome of mean change from baseline in best-corrected visual acuity, the manufacturer repeated the analysis after excluding one study (DETAIL study; London et al. 2009) because patients in the study responded differently to ranibizumab in a 'treatment as needed' regimen compared with other studies.

- 3.9 The manufacturer presented separate network meta-analyses for outcomes at 12 months, 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. These analyses showed no statistically significant differences between aflibercept 2 mg every 8 weeks and ranibizumab 0.5 mg treatment as needed in the proportion of patients who maintained vision (frequentist method: odds ratio [OR] 1.44, 95% CI 0.68 to 3.09; Bayesian method: OR 1.51, 95% CI 0.42 to 5.94) or gained vision (frequentist method: OR 1.29, 95% CI 0.91 to 1.83; Bayesian method: OR 1.28, 95% CI 0.45 to 3.68). No statistically significant differences in mean change in best-corrected visual acuity at 12 months were shown between aflibercept 2 mg every 8 weeks and ranibizumab 0.5 mg treatment as needed (frequentist method: mean difference 0.83, 95% CI -1.57 to 3.23; Bayesian method: mean difference -2.87, 95% CI -10.02 to 4.30). When the manufacturer repeated the analysis after excluding the DETAIL study, the results for the outcome of mean change in best-corrected visual acuity at 12 months were similar (frequentist method: mean difference 1.35, 95% CI -1.08 to 3.77; Bayesian method: mean difference 1.15, 95% CI -3.92 to 6.09).
- 3.10 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 every 8 weeks to a treatment as needed regimen (aflibercept fixed 2 mg every

8 weeks/treatment as needed). Therefore, two-step indirect comparisons, based on the Bucher method, were used to compare aflibercept fixed 2 mg every 8 weeks/treatment as needed with ranibizumab 0.5 mg treatment as needed. The indirect comparisons included data from 3 studies: VIEW 1 and 2, and CATT, a 2-year study that compared ranibizumab 0.5 mg with bevacizumab for treating 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 treatment as needed only. Both sets of data from the CATT study were analysed for the indirect comparison.

- 3.11 The results of the manufacturer's indirect comparison for the outcomes at 24 months also showed no statistically significant differences between aflibercept fixed 2 mg every 8 weeks/treatment as needed and ranibizumab 0.5 mg treatment as needed in the proportion of patients who maintained vision (relative risk 0.99, 95% CI 0.93 to 1.07) or gained vision (relative risk 0.88, 95% CI 0.61 to 1.28). No statistically significant differences in mean change in best-corrected visual acuity at 24 months were shown between aflibercept 2 mg every 8 weeks and ranibizumab 0.5 mg treatment as needed (mean difference 0.31, 95% CI -4.33 to 3.71).
- 3.12 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, treatment as needed re-treatment criteria, proportion of men, 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.
- 3.13 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: conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%). The incidence of arterial thromboembolic events (including non-fatal myocardial infarction, non-fatal stroke or vascular stroke), which are potentially related to anti-VEGF treatment, was also similar between the aflibercept (3.3%) and ranibizumab (3.2%) treatment groups in VIEW 1 and 2.

## Cost effectiveness

- 3.14 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 every 8 weeks or ranibizumab 0.5 mg treatment as needed. 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%.
- 3.15 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 on the ETDRS scale, ranging from no visual impairment (ETDRS more than 80 letters) to blindness (ETDRS fewer than 36 letters) with 3 intermediate levels (ETDRS 66–80 letters; 51–65 letters and 36–50 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 2 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.

- 3.16 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 improving and maintaining vision for aflibercept compared with ranibizumab taken from the manufacturer's network meta-analysis and indirect comparison of aflibercept 2 mg every 8 weeks with ranibizumab 0.5 mg treatment as needed. During this period, people who were defined as being in the blind health state received treatment with ranibizumab or aflibercept. However, 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). The annual rates of treatment discontinuation in year 1 (2.7%) and year 2 (3.5%) 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.
- 3.17 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 statistically 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 the annual probability of treatment discontinuation in years 3 to 5 (18.7%), which were also assumed to be identical between treatment groups. From year 6 it was assumed that all people in both treatment groups discontinued active treatment and

started best supportive care.

- 3.18 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 letters (0.56%) or 30 letters (1.56%) with the remaining people maintaining stable visual acuity.
- 3.19 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 from UK life tables was used for both treatment groups. For people who were blind in both eyes, an excess risk of mortality was taken from a UK study of older patients with visual impairment (Thiagarajan et al. 2005).
- 3.20 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 dataset 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 consistently 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. The resulting utility values applied in the model are academic in confidence and therefore not reported here. 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 health-related quality of life 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 utility decrements were subtracted from the utility values for the health states defined by visual acuity and included retinal haemorrhage (-0.300), vitreous haemorrhage (-0.305), endophthalmitis (-0.300), cataract (-0.142) and retinal detachment (-0.27).

- 3.21 The manufacturer included the costs of drug treatment, including drug acquisition, administration and monitoring costs. The drug acquisition costs incorporated the confidential discount applied to the list price of aflibercept approved as part of the patient access scheme. The manufacturer of ranibizumab has also previously agreed a revised patient access scheme with the Department of Health in 2013 (as revised in the context of [NICE technology appraisal guidance 274](#)), in which it applied a revised discount to ranibizumab for all indications. At the time of submission for this appraisal, the manufacturer of aflibercept was unaware of the size of the confidential discount and 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%.
- 3.22 The resource use and unit costs associated with treatment and monitoring visits were based on Hospital Episode Statistics (HES 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 that 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 fluorescein angiography (£117) before starting treatment.

3.23 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 European Medicines Agency assessment report for the 2011 revision of the summary of product characteristics. Based on clinical specialist opinion, the manufacturer assumed that people in both treatment groups had 4 injections in years 3 to 5.

3.24 The manufacturer assumed that separate 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. People receiving aflibercept had 7 monitoring visits in year 1 and 6 monitoring visits in year 2 and people receiving ranibizumab had 12 monitoring visits in years 1 and 2. People receiving aflibercept in a one-stop model had their treatment and monitoring at the same visit and therefore needed no separate monitoring visits in the first year and 2 separate visits in the second year. People receiving aflibercept in a two-stop model in the second year had their treatment and monitoring at separate visits and therefore needed 6 separate monitoring visits in the second year. People receiving ranibizumab had 4 separate monitoring visits in the first year and 6 separate visits in the second year in a one-stop model and 12 separate monitoring visits in the first 2 years in a two-stop model. On the basis of clinical specialist opinion, people in years 3 to 5 in both treatment groups had 3 separate monitoring visits in the one-stop model and 7 separate monitoring visits in a two-stop model.

- 3.25 The manufacturer estimated the costs associated with blindness for people who were defined as being blind in both eyes (ETDRS score under 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.
- 3.26 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 because it resulted in lower costs and higher quality-adjusted life years (QALYs; 7.77 compared with 7.76). When the manufacturer applied a discount to the list price of ranibizumab, ranging from 10 to 50%, aflibercept continued to dominate ranibizumab.
- 3.27 The manufacturer performed one-way sensitivity analysis using a net monetary benefit approach because aflibercept dominated ranibizumab in the base-case analysis<sup>[1]</sup>. The deterministic and probabilistic sensitivity analyses used the discounted price for aflibercept agreed under the patient access scheme and the list 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. The manufacturer stated that, in all sensitivity analyses, aflibercept continued to dominate ranibizumab. Results of the manufacturer's probabilistic sensitivity analysis showed that aflibercept had a 100% probability of being cost effective compared with ranibizumab if the maximum acceptable incremental cost-effectiveness ratio (ICER) was £20,000 per QALY gained.
- 3.28 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).

## ERG critique of manufacturer's submission

3.29 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 manufacturer used the last observation carried forward approach to calculate missing data for the primary outcome of the proportion of people 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. After clarification, the manufacturer provided the observed results at week 52 for the outcome of maintained vision from the per protocol and full analysis datasets, which were similar to the original 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 were similar to 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.

- 3.30 The ERG agreed with the manufacturer that there were concerns about 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.
- 3.31 In its critique of the manufacturer's economic model, 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 people 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.

- 3.32 The ERG noted that people 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 that the dosing schedule suggests that people 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 noted that the average number of 4 aflibercept injections in year 2 of the model, which were taken from the VIEW 2 study, had been annualised from 44 weeks to 52 weeks to account for the study duration (96 weeks) which was slightly shorter than 2 years (104 weeks). The ERG considered that, on the basis of the weighted average number of injections of ranibizumab (7.4) 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 probably have been 7 rather than 8. The ERG commented that the network meta-analysis for visual acuity outcomes at 24 months relied largely upon data from the CATT study, in which patients treated with ranibizumab had an average of 5.7 injections in a 'treatment as needed' regimen in year 2. The ERG therefore considered that the manufacturer's assumption of 6 ranibizumab injections in the second year of the model was reasonable.
- 3.33 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.

- 3.34 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.
- 3.35 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 resulting impact on health-related quality of life. The ERG considered that the manufacturer's assumption of no 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 a narrower range of utility values 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 under the assumption of the worse-seeing eye being blind.

- 3.36 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. If patients in the aflibercept group followed a two-stop model, they would therefore have 7 separate monitoring visits in year 1. 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 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 274), 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 fluorescein 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.
- 3.37 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 treatment 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 3.35) 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.

- 3.38 The ERG applied the changes outlined in section 3.37 in 2 scenario analyses for the worse-seeing eye model and 2 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.
- 3.39 The ERG incorporated the confidential discount applied to the list price of aflibercept and a range of discounts (from 0 to 50% in increments of 5%) to the list price of ranibizumab in its scenario analyses as outlined in section 3.38. In the ERG's first scenario analysis for the worse-seeing eye model, aflibercept either dominated ranibizumab (discount 0–45%) or resulted in an ICER of £60,153 per QALY gained (discount 50%). In the ERG's first scenario analysis for the better-seeing eye model, aflibercept either dominated ranibizumab (discount 0–45%) or resulted in an ICER of £9002 per QALY gained (discount 50%). In the ERG's second scenario analysis for the worse-seeing eye model, aflibercept resulted in lower costs and lower QALYs compared with ranibizumab when a discount range of 0–45% was applied to the list price of ranibizumab, with ICERs ranging from £1,692,511 to £108,180 saved per QALY lost. In the ERG's second scenario analysis for the better-seeing eye model, the ICERs for aflibercept compared with ranibizumab ranged from £261,432 to £16,710 saved per QALY lost when a discount range of 0–45% was applied to the list price ranibizumab. When the ERG applied a 50% discount to the list price of ranibizumab, aflibercept was dominated by ranibizumab for both the worse-seeing eye and better-seeing eye models.
- 3.40 Full details of all the evidence are in the [manufacturer's submission](#) and the [ERG report](#).

<sup>[1]</sup> Net monetary benefit = (£20,000 × incremental QALYs) – incremental costs

## 4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of aflibercept solution for injection, having considered evidence on the nature of wet age-related macular degeneration and the value placed on the benefits of aflibercept by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the patient experts that visual impairment has a substantial negative impact on the physical and emotional wellbeing of people with wet age-related macular degeneration. The patient experts stated that the condition affects their ability to work and other leisure activities and in turn, can increase the risk of depression and social isolation. The patient experts also acknowledged that, despite any initial anxiety about having an injection in the eye, they are willing to receive injections in order to prevent sight loss. The Committee agreed that loss of vision caused by wet age-related macular degeneration can substantially impair health-related quality of life.

4.2 The Committee discussed the currently available treatments and the likely place of aflibercept in treating wet age-related macular degeneration. The Committee heard from the clinical specialists that the current standard treatment for wet age-related macular degeneration is ranibizumab as a consequence of [NICE technology appraisal guidance 155](#). It also heard that, in some NHS trusts and private clinical practice, both ranibizumab and bevacizumab for intravitreal use are used on the basis of economic considerations. However, the clinical specialists explained that people treated with ranibizumab and bevacizumab should have their condition monitored every 4 weeks and that very few NHS trusts were able to manage wet age-related macular degeneration at such regular intervals. They also stated that people usually receive 6 ranibizumab injections in the first year of treatment rather than up to 12 injections seen in the clinical trials. The clinical specialists commented that data from several UK ophthalmology departments suggest that the current ranibizumab treatment regimen is inadequate and so visual acuity outcomes may be inferior to results reported in the clinical trials. However, the Committee also acknowledged that these inferior visual

acuity outcomes could be attributed to the widening range of disease severity seen in clinical practice. The Committee understood from the clinical specialists that an important advantage of aflibercept is that it needs less frequent administration than ranibizumab while achieving similar clinical outcomes, as seen in the clinical trials, thus imposing less burden on NHS capacity. The Committee also understood from the patient experts that, because aflibercept is associated with fewer treatment and monitoring visits, it will reduce the burden on patients and their carers in terms of time off work and travel costs.

- 4.3 The Committee considered the manufacturer's decision to exclude bevacizumab for intravitreal use as a comparator in its submission, despite being listed as a comparator in the scope. It was aware that bevacizumab does not have a UK marketing authorisation for treating wet age-related macular degeneration. However, the Committee noted that a marketing authorisation is not a prerequisite for a comparator in a NICE technology appraisal. It noted that NICE's [Guide to the methods of technology appraisal](#), in recommending comparison with technologies that are 'best practice' or in 'routine use', is not intended to be restrictive but to emphasise the need for comparison with all relevant comparators; any medicine in routine use or considered to be best practice should be considered a potential comparator. The Committee also noted advice from the NICE Board that the decision to include bevacizumab as a comparator should be based on both a careful consideration of its use in clinical practice for wet age-related macular degeneration and a thorough assessment of its efficacy, quality and safety. The Committee was aware of recently published evidence from the IVAN and CATT trials comparing the clinical efficacy and safety of bevacizumab with ranibizumab in people with wet age-related macular degeneration, which has addressed some of these issues. However, the Committee acknowledged that bevacizumab was not included as a comparator treatment in the appraisal of [ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#) (NICE technology appraisal guidance 155), and that this appraisal was undertaken before the emergence of evidence on the clinical effectiveness of bevacizumab. Therefore, the Committee agreed that it was reasonable to defer consideration of bevacizumab as a comparator in this appraisal. In the interests of fairness, it also agreed that the proposed review of the

guidance on aflibercept should coincide with the review date for NICE technology appraisal guidance 155, which should also include bevacizumab (see [section 7](#)).

- 4.4 The Committee considered the manufacturer's decision to exclude photodynamic therapy as a comparator in its submission, despite being listed as a comparator in the scope. The Committee noted from the manufacturer that, although [NICE technology appraisal guidance 68](#) recommended photodynamic therapy for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation, clinical practice has subsequently changed for this group and that newer treatments, including anti-vascular endothelial growth factor (VEGF) therapies have superseded photodynamic therapy. The Committee heard from the clinical specialists that photodynamic therapy is currently used in combination with an anti-VEGF therapy for treating wet age-related macular degeneration in people with polypoidal choroidal vasculopathy whose condition does not respond to initial anti-VEGF therapy (approximately 10–15% of patients). Therefore, the Committee considered that photodynamic therapy would only be offered as a second-line treatment option after first-line anti-VEGF therapy for this group of people and concluded that it was reasonable to exclude photodynamic therapy as a comparator in this appraisal.

## Clinical effectiveness

- 4.5 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of aflibercept. The Committee noted that the main sources of evidence came from the VIEW 1 and 2 trials which compared aflibercept (2 mg every 8 weeks) with ranibizumab (0.5 mg every 4 weeks) in people with wet age-related macular degeneration and that both studies were considered to be of high quality by the Evidence Review Group (ERG). It also noted that aflibercept at its licensed dose was shown to be clinically non-inferior to ranibizumab in terms of visual acuity outcomes at 96 weeks. The Committee concluded that aflibercept is a clinically effective treatment option for visual impairment caused by wet age-related macular degeneration.

- 4.6 The Committee considered the network meta-analyses and indirect comparisons submitted by the manufacturer, which estimated the clinical effectiveness of aflibercept at its licensed dose compared with ranibizumab in a 'treatment as needed' regimen at 12 and 24 months. The Committee accepted the concerns highlighted by the manufacturer and the ERG about the validity of these analyses because of the heterogeneity of the included studies. It was also aware that, although the point estimates for visual acuity outcomes favoured aflibercept, no statistically significant differences compared with ranibizumab were reported. The Committee concluded that, in the absence of stronger evidence, the results could be used to inform decisions about the clinical effectiveness of aflibercept compared with ranibizumab in a 'treatment as needed' regimen.
- 4.7 The Committee considered the evidence for adverse events associated with aflibercept. The Committee noted that the frequency of adverse events in both treatment groups in the VIEW 1 and 2 trials was low. The Committee noted that the manufacturer had not provided a formal statistical analysis comparing adverse events between the 2 treatment groups. However, it also noted that no clinically meaningful differences in adverse events were reported by the manufacturer or the ERG. The Committee concluded that aflibercept was safe and well tolerated in patients with wet age-related macular degeneration.

## Cost effectiveness

- 4.8 The Committee considered the manufacturer's economic model and the ERG's critique and exploratory analyses. The Committee noted that the model structure accounted for different levels of visual acuity in both eyes rather than the first eye to come to clinical attention. The Committee also noted the ERG's concerns about the manufacturer's approach to modelling second-eye involvement. The Committee agreed with the ERG that it was unrealistic to assume no second-eye involvement in the first 2 years of the model because a large proportion of patients in the VIEW 1 and 2 trials had visual impairment in their second eye at the start of treatment. It also agreed that the manufacturer did not give appropriate consideration to the timing of second-eye involvement because the effect of treatment on visual acuity

in the second eye and any associated costs were limited to years 3 to 5 in the model. The Committee concluded that the ERG's exploratory approach, which involved separate analyses depending on whether the study eye was a better-seeing eye or worse-seeing eye, was more reasonable.

4.9 The Committee discussed the clinical-effectiveness data that were used in the economic model. The Committee noted that clinical-effectiveness data for aflibercept were derived from the VIEW 2 study only rather than from a pooled analysis of the VIEW 1 and 2 studies. The Committee heard from the manufacturer that this was because VIEW 2 was conducted across multiple centres including the UK and therefore was more relevant to UK clinical practice than the VIEW 1 study, and also because the EQ-5D utility values used in the model were collected in the VIEW 2 study. The Committee agreed that using clinical-effectiveness data from VIEW 1 only was unlikely to introduce any additional bias because results were similar between VIEW 1 and 2 and a pooled analysis of both studies. The Committee also noted the ERG's comments that the manufacturer had applied comparative clinical-effectiveness data in terms of visual acuity from its network meta-analyses and indirect comparisons between baseline and 12 months and between 12 months and 24 months rather than between baseline and 12 months and between baseline and 24 months. It noted that this resulted in aflibercept having better visual acuity than ranibizumab at 24 months in the model although the point estimates from the indirect comparison showed that aflibercept resulted in slightly worse outcomes. The Committee agreed with the ERG that the results of the manufacturer's indirect comparison at 24 months provided comparative clinical-effectiveness data between baseline and 24 months, and it concluded that the ERG's exploratory analysis that incorporated this data was the preferred approach.

4.10 The Committee discussed the manufacturer's assumptions about the number of treatment and monitoring visits people in both treatment groups needed in the model. The Committee considered that, in the absence of any longer-term data, it was reasonable for the manufacturer to assume that both treatment groups would have the same number of treatment and monitoring visits in years 3 to 5 of the model. The Committee noted that the manufacturer assumed that people receiving

aflibercept had 7 treatment visits in the first year based on the summary of product characteristics. However, the Committee agreed with the ERG that it was more likely that people treated with aflibercept would need 8 treatment visits in the first year of the model on the basis of the average number of injections that patients received in the VIEW 2 study. It also noted that the ERG had corrected for this in its exploratory analyses. The Committee was aware that there are data from UK clinical practice on the treatment and monitoring frequency of ranibizumab but that no such data on the use of aflibercept currently exist. For this reason, the Committee considered that it would be fairer to use the same data that were used to estimate the relative clinical effectiveness of aflibercept and ranibizumab to inform assumptions about the number of treatment and monitoring visits in the model. Therefore, the Committee concluded that it was reasonable to assume that people in both treatment groups would need 8 treatment visits in the first year of the model in line with the approach taken by the ERG in its exploratory analyses.

- 4.11 The Committee discussed the manufacturer's assumptions about whether treatment administration and monitoring occurred at the same visit. The Committee noted that the manufacturer had assumed that, in the first year of the model, people in the aflibercept group had their treatment administration and monitoring at the same visit in a one-stop model but 50% of people in the ranibizumab group had separate monitoring visits in a two-stop model. The Committee heard from the clinical specialists that, in future clinical practice, it is expected that fewer people treated with anti-VEGF therapies would need separate treatment and monitoring visits. The Committee noted that, if a higher proportion of people in both treatment groups had their treatment administration and monitoring at the same visit, this would reduce the total incremental costs of ranibizumab compared with aflibercept because of the higher number of monitoring visits needed by people treated with ranibizumab in the first 2 years of the manufacturer's model. However, the Committee agreed that, for people who had their treatment and monitoring at the same visit in a one-stop model, the aflibercept group had no separate monitoring visits in the first year and 2 separate visits in the second year and the ranibizumab group had 4 separate monitoring visits in the first year and 6 separate visits in the second year.

The Committee also agreed that, for people who had their treatment and monitoring at separate visits in a two-stop model, the aflibercept group had 7 separate monitoring visits in the first year and 6 separate monitoring visits in the second year and the ranibizumab group had 12 separate monitoring visits in the first 2 years. The Committee concluded that, based on current clinical practice, it was reasonable to assume that 50% of people in both treatment groups would need separate monitoring visits in line with the approach taken by the ERG in its exploratory analyses.

4.12 The Committee discussed the manufacturer's assumptions about the costs of treatment and monitoring visits. The Committee noted that the manufacturer's estimated cost per treatment visit was higher than the cost used in the appraisal of [ranibizumab for the treatment of diabetic macular oedema](#) (NICE technology appraisal guidance 274) and that the ERG also estimated a lower average cost per treatment visit of £129. However, the Committee heard from the clinical specialists that the ERG's lower estimate was likely to be an underestimate of the true costs of a treatment visit. The Committee also heard from the clinical specialists that the ERG's estimated cost for optical coherence tomography of £51 as part of a monitoring visit was probably too low. Overall, the Committee concluded that although some uncertainty remained about the true costs involved in treatment and monitoring visits for people with wet age-related macular degeneration, the estimates used in the ERG's exploratory analyses were a fair reflection of the costs involved.

4.13 The Committee considered the incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer and the ERG, which incorporated the confidential discounts applied to the list prices of aflibercept and ranibizumab agreed under the respective patient access schemes. The Committee noted that, in the manufacturer's base-case analysis, aflibercept dominated (that is, was less expensive and more effective than) ranibizumab. The Committee also considered its preferred analyses based on the ERG's exploratory approach, which incorporated separate analyses depending on whether the study eye was a better-seeing eye or a worse-seeing eye, and its preferred assumptions about the frequency of injections, monitoring visits and clinical-effectiveness data

(see sections 4.8 to 4.11). It noted that these exploratory analyses incorporated the confidential discount to the list price of aflibercept and a range of discounts (from 0 to 50%) to the list price of ranibizumab. The Committee also noted that, when discounts to the list price of ranibizumab ranged from 0 to 45%, aflibercept had lower costs and quality-adjusted life years (QALYs) than ranibizumab, which resulted in ICERs for aflibercept compared with ranibizumab ranging from £1,690,000 to £16,700 saved per QALY lost and that, when a 50% discount was applied to the list price of ranibizumab, aflibercept was dominated by ranibizumab in both the worse-seeing eye and better-seeing eye models (see section 3.39). However, the Committee was aware that, in both the manufacturer's and the ERG's analyses, the differences in total costs and QALYs were very small. The Committee therefore concluded that aflibercept could be recommended as a cost-effective use of NHS resources if ranibizumab would otherwise be the treatment used.

- 4.14 The Committee discussed whether aflibercept solution for injection should be recommended within the terms of its UK marketing authorisation, that is, for the treatment of neovascular (wet) age-related macular degeneration, or whether a more restrictive set of criteria was necessary. The Committee noted that guidance on the use of ranibizumab outlined in [NICE technology appraisal guidance 155](#) was based on a more restrictive set of criteria than described in the terms of its UK marketing authorisation and that these criteria were set out in the clinical trials for ranibizumab for treating wet age-related macular degeneration. It also noted that these criteria were very similar to those set out in the VIEW 1 and 2 studies. The Committee also heard from the clinical specialists that they would prefer that the use of aflibercept should not be restricted to people with a best-corrected visual acuity between 6/12 and 6/96, as is the case with ranibizumab in NICE technology appraisal guidance 155. However, the Committee concluded that it would be appropriate to recommend aflibercept as a treatment option for people with wet age-related macular degeneration if it is used according to the same criteria as described for the use of ranibizumab in NICE technology appraisal guidance 155 until both technologies could be appraised simultaneously in the context of a multiple technology appraisal.

- 4.15 The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It agreed that anti-VEGF treatments were a substantial improvement over previous treatments, but considered that this improvement applied to the class of drugs, including bevacizumab. It stated that the innovation was in the development of anti-VEGF treatments, not the act of licensing. In addition the Committee was not aware of any substantial benefits of aflibercept compared with ranibizumab that had not already been captured in the manufacturer's economic model.
- 4.16 The Committee considered whether there were any equality considerations affecting population groups protected by equality legislation and concluded that there were no equality issues relating to this appraisal in the guidance.

## Summary of Appraisal Committee's key conclusions

TA294	Appraisal title: Aflibercept solution for injection for treating wet age-related macular degeneration	Section
<b>Key conclusion</b>		
Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if it is used in accordance with the recommendations for ranibizumab in <a href="#">NICE technology appraisal guidance 155</a> (re-issued in May 2012) and the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.		1.1

<p>The Committee noted that its preferred analyses incorporated the confidential discount to the list price of aflibercept and a range of discounts (from 0 to 50%) to the list price of ranibizumab. It also noted that, when discounts to the list price of ranibizumab ranged from 0 to 45%, aflibercept had lower costs and quality-adjusted life years (QALYs) than ranibizumab, which resulted in ICERs for aflibercept compared with ranibizumab ranging from £1,690,000 to £16,700 saved per QALY lost and that, when a 50% discount was applied to the list price of ranibizumab, aflibercept was dominated by ranibizumab in both the worse-seeing eye and better-seeing eye models. However, the Committee was aware that, in both the manufacturer's and the ERG's analyses, the differences in total costs and QALYs were very small. The Committee therefore concluded that aflibercept could be recommended as a cost-effective use of NHS resources if ranibizumab would otherwise be the treatment used.</p>		4.13
<p><b>Current practice</b></p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee agreed that loss of vision caused by wet age-related macular degeneration can substantially impair health-related quality of life.</p>	4.1
	<p>The Committee heard from the clinical specialists that the current standard treatment for wet age-related macular degeneration is ranibizumab as a consequence of <a href="#">NICE technology appraisal guidance 155</a>.</p>	4.2
<p><b>The technology</b></p>		
<p>Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee understood from the clinical specialists that an important advantage of aflibercept is that it needs less frequent administration than ranibizumab while achieving similar clinical outcomes, as seen in the clinical trials, thus imposing less burden on NHS capacity.</p>	4.2
	<p>The Committee was not aware of any substantial benefits of aflibercept compared with ranibizumab that had not already been captured in the manufacturer's economic model.</p>	4.15

What is the position of the treatment in the pathway of care for the condition?	Aflibercept solution for injection has a UK marketing authorisation 'for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)'.	2.1
Adverse reactions	The Committee concluded that aflibercept was safe and well tolerated in patients with wet age-related macular degeneration.	4.7
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee noted that the main sources of evidence came from the VIEW 1 and 2 trials which compared aflibercept (2 mg every 8 weeks) with ranibizumab (0.5 mg every 4 weeks) in people with wet age-related macular degeneration and that both studies were considered to be of high quality by the Evidence Review Group (ERG).	4.5
	For the comparison of aflibercept at its licensed dose with ranibizumab in a 'treatment as needed' regimen at 12 and 24 months, the Committee accepted the concerns highlighted by the manufacturer and the ERG about the validity of the manufacturer's network meta-analyses and indirect comparisons because of the heterogeneity of the included studies. The Committee concluded that, in the absence of stronger evidence, the results could be used to inform decisions about the clinical effectiveness of aflibercept compared with ranibizumab in a 'treatment as needed' regimen.	4.6

<p>Relevance to general clinical practice in the NHS</p>	<p>The clinical specialists explained that people treated with ranibizumab and bevacizumab should have their condition monitored every 4 weeks and that very few NHS trusts were able to manage wet age-related macular degeneration at such regular intervals. They also stated that patients usually receive 6 ranibizumab injections in the first year of treatment rather than up to 12 injections seen in the clinical trials. The clinical specialists commented that data from several UK ophthalmology departments suggest that the current ranibizumab treatment regimen is inadequate and so visual acuity outcomes may be inferior to results reported in the clinical trials. However, the Committee also acknowledged that these inferior visual acuity outcomes could be attributed to the widening range of disease severity seen in clinical practice.</p>	<p>4.2</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee acknowledged that bevacizumab was not included as a comparator treatment in the appraisal of <a href="#">ranibizumab and pegaptanib for the treatment of age-related macular degeneration</a> (NICE technology appraisal guidance 155), although this was undertaken before the emergence of evidence on the clinical effectiveness of bevacizumab. Therefore, the Committee agreed that it was reasonable to defer consideration of bevacizumab as a comparator in this appraisal. In the interests of fairness, it also agreed that the proposed review of the guidance on aflibercept should coincide with the review date for NICE technology appraisal guidance 155, which should also include bevacizumab.</p>	<p>4.3</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>None was identified.</p>	<p>–</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that aflibercept at its licensed dose was shown to be clinically non-inferior to ranibizumab in terms of visual acuity outcomes at 96 weeks. The Committee concluded that aflibercept is a clinically effective treatment option for visual impairment caused by wet age-related macular degeneration.</p>	<p>4.5</p>
	<p>For the network meta-analyses and indirect comparisons submitted by the manufacturer, the Committee was aware that, although the point estimates for visual acuity outcomes favoured aflibercept, no statistically significant differences with ranibizumab were reported.</p>	<p>4.6</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The Committee considered the manufacturer's economic model and the ERG's critique and exploratory analyses. The Committee agreed with the ERG that it was unrealistic to assume no second-eye involvement in the first 2 years of the model because a large proportion of patients in the VIEW 1 and 2 trials had visual impairment in their second eye at the start of treatment. The Committee concluded that the ERG's exploratory approach, which involved separate analyses depending on whether the study eye was a better-seeing eye or worse-seeing eye, was more reasonable.</p>	<p>4.8</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted the ERG's comments that the manufacturer had applied comparative clinical-effectiveness data in terms of visual acuity from its network meta-analyses and indirect comparisons between baseline and 12 months and between 12 months and 24 months rather than between baseline and 12 months and between baseline and 24 months. The Committee agreed with the ERG that the results of the manufacturer's indirect comparison at 24 months provided comparative clinical-effectiveness data between baseline and 24 months, and it concluded that the ERG's exploratory analysis that incorporated this data was the preferred approach.</p>	<p>4.9</p>

	<p>The Committee concluded that it was reasonable to assume that people in both treatment groups would need 8 treatment visits in the first year of the model in line with the approach taken by the ERG in its exploratory analyses.</p>	4.10
	<p>The Committee concluded that, based on current clinical practice, it was reasonable to assume that 50% of people in both treatment groups would need separate monitoring visits in line with the approach taken by the ERG in its exploratory analyses.</p>	4.11
	<p>The Committee concluded that although some uncertainty remained about the true costs involved in treatment and monitoring visits for people with wet age-related macular degeneration, the estimates used in the ERG's exploratory analyses were a fair reflection of the costs involved.</p>	4.12
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>No specific conclusions were made by the Committee about health-related quality-of-life benefits and utility values.</p>	–
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>None was identified.</p>	–

<p>What are the key drivers of cost effectiveness?</p>	<p>The results of the manufacturer's 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.</p>	<p>3.27</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee noted that its preferred analyses incorporated the confidential discount to the list price of aflibercept and a range of discounts (from 0 to 50%) to the list price of ranibizumab. It also noted that, when discounts to the list price of ranibizumab ranged from 0 to 45%, aflibercept had lower costs and quality-adjusted life years (QALYs) than ranibizumab, which resulted in ICERs for aflibercept compared with ranibizumab ranging from £1,690,000 to £16,700 saved per QALY lost and that, when a 50% discount was applied to the list price of ranibizumab, aflibercept was dominated by ranibizumab in both the worse-seeing eye and better-seeing eye models. However, the Committee was aware that, in both the manufacturer's and the ERG's analyses, the differences in total costs and QALYs were very small.</p>	<p>4.13</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The manufacturer of aflibercept solution for injection has agreed a patient access scheme with the Department of Health. This involves a confidential discount applied to the list price of aflibercept solution for injection. The level of the discount is commercial in confidence.</p>	<p>2.4</p>
<p>End-of-life considerations</p>	<p>Not applicable.</p>	<p>–</p>
<p>Equalities considerations and social value judgements</p>	<p>The Committee considered whether there were any equalities considerations affecting population groups protected by equality legislation and concluded that there were no equality issues relating to this appraisal in the guidance.</p>	<p>4.16</p>

## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has wet age-related macular degeneration and the doctor responsible for their care thinks that aflibercept solution for injection is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 The Department of Health and the manufacturer have agreed that aflibercept solution for injection will be available to the NHS with a patient access scheme which makes aflibercept solution for injection available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [lesley.gilmour@bayer.com](mailto:lesley.gilmour@bayer.com).
- 5.4 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing template and report to estimate the national and local savings and costs associated with implementation.

## 6 Related NICE guidance

- [Epiretinal brachytherapy for wet age related macular degeneration](#). NICE interventional procedure guidance 415 (2011).
- [Macular translocation with 360° retinotomy for wet age-related macular degeneration](#). NICE interventional procedure guidance 340 (2010).
- [Limited macular translocation for wet age-related macular degeneration](#). NICE interventional procedure guidance 339 (2010).
- [Implantation of miniature lens systems for advanced age-related macular degeneration](#). NICE interventional procedure guidance 272 (2008).
- [Ranibizumab and pegaptanib for the treatment of age-related macular degeneration](#). NICE technology appraisal guidance 155 (2008).
- [Transpupillary thermotherapy for age-related macular degeneration](#). NICE interventional procedure guidance 58 (2004).
- [Radiotherapy for age-related macular degeneration](#). NICE interventional procedure guidance 49 (2004).
- [Guidance on the use of photodynamic therapy for age-related macular degeneration](#). NICE technology appraisal guidance 68 (2003).

## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in February 2014. This is to coincide with the review date proposed for NICE technology appraisal guidance 155 (ranibizumab and pegaptanib for the treatment of age-related macular degeneration). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon  
Chief Executive  
July 2013

## 8 Appraisal Committee members and NICE project team

### 8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

#### **Professor Gary McVeigh**

Vice Chair of Appraisal Committee C, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

#### **Professor Kathryn Abel**

Director of Centre for Women's Mental Health, University of Manchester

#### **Dr Daniele Bryden**

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

#### **Dr Andrew Burnett**

Director for Health Improvement and Medical Director, NHS Barnet, London

**David Chandler**

Lay Member

**Gail Coster**

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

**Professor Peter Crome**

Honorary Professor, Dept of Primary Care and Population Health, University College London

**Dr Maria Dyban**

General Practitioner, Kings Road Surgery, Glasgow

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Greg Fell**

Consultant in Public Health, Bradford Metropolitan Borough Council

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Dr Janice Kohler**

Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

**Emily Lam**

Lay Member

**Dr Allyson Lipp**

Principal Lecturer, University of Glamorgan

**Dr Claire McKenna**

Research Fellow in Health Economics, University of York

**Dr Grant Maclaine**

Director, Health Economics & Outcomes Research, BD, Oxford

**Dr Andrea Manca**

Health Economist and Senior Research Fellow, University of York

**Henry Marsh**

Consultant Neurosurgeon, St George's Hospital, London

**Dr Suzanne Martin**

Reader in Health Sciences

**Dr Paul Miller**

Director, Payer Evidence, AstraZeneca UK Ltd

**Professor Eugene Milne**

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Dr Anna O'Neill**

Deputy Head of Nursing and Healthcare School/Senior Clinical University Teacher, University of Glasgow

**Alan Rigby**

Academic Reader, University of Hull

**Dr Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Dr Tim Stokes**

Senior Clinical Lecturer, University of Birmingham

**Dr Paul Tappenden**

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

**Dr Judith Wardle**

Lay Member

## 8.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Matthew Dyer**

Technical Lead

**Zoe Charles**

Technical Adviser

**Lori Farrar**

Project Manager

## 9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:

- Cummins E, Fielding S, Johnston R, Rothnie K, Stewart F, Lois N, Burr J, Brazzelli M. Aflibercept solution for injection for the treatment of wet age-related macular degeneration. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on Aflibercept solution for injection for the first line treatment of wet age-related macular degeneration (AMD) by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor

- Bayer

II. Professional/specialist and patient/carers groups:

- Macular Society
- Royal National Institute of Blind People (RNIB)
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Pathologists

III. Other consultees:

- Department of Health

- Bristol, North Somerset and South Gloucestershire (PCT Cluster)
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Moorfields Pharmaceuticals
- Novartis Pharmaceuticals
- Aberdeen HTA Group
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on aflibercept by providing oral evidence to the Committee.

- Ian Pearce, Consultant Ophthalmologist, nominated by RNIB – clinical specialist
- Robert Johnson, Consultant Ophthalmologist, nominated by Bayer – clinical specialist
- Sobha Sivaprasad, Consultant Ophthalmologist, nominated by The Royal College of Ophthalmologists - clinical specialist
- Cathy Yelf, nominated by Macular Society - patient expert
- Clara Eaglan, nominated by RNIB - patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bayer

# Changes after publication

**January 2014:** minor maintenance

# About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

## Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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