

Aflibercept for treating diabetic macular oedema

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 visual impairment caused by diabetic macular oedema only if:
- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
 - the company provides aflibercept with the discount agreed in the patient access scheme.
- 1.2 People whose treatment with aflibercept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue aflibercept until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Aflibercept (Eylea, Bayer Pharma) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein that binds to all forms of VEGF-A, VEGF-B, and the placental growth factor. VEGF is involved in the pathogenesis of diabetic macular oedema (DMO). Aflibercept has a UK marketing authorisation for 'the treatment of adults with visual impairment due to diabetic macular oedema'.
- 2.2 In the summary of product characteristics the most frequent adverse reactions to aflibercept treatment include subconjunctival haemorrhage (bleeding under the membrane covering the white of the eye), reduction in visual acuity, eye pain at the injection site, an increase in intraocular pressure and cataract formation. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Aflibercept is given as a single 2 mg intravitreal injection every month for 5 consecutive months, followed by 1 injection every 2 months with no requirement for monitoring between visits. After the first 12 months, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician. Aflibercept should be discontinued if the patient is not benefiting from continued treatment.
- 2.4 The list price of aflibercept is £816.00 per vial (excluding VAT; British national formulary [BNF] edition January 2015). The total cost for treating a patient in the first year is £6936 (based on 8.5 aflibercept injections). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of aflibercept, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee ([section 7](#)) considered evidence submitted by the company on aflibercept and a review of this submission by the Evidence Review Group (ERG; [section 8](#)).

Clinical effectiveness

- 3.1 The main sources of evidence presented in the company's submission came from 2 ongoing phase-III trials: VIVID and VISTA. VISTA (n=466) is a double-blind, randomised (1:1:1) active-controlled superiority study carried out at 54 sites in the USA. VIVID (n=406) is an ongoing prospective, randomised, double-blind, active-controlled superiority study carried out at 73 sites across Japan, Europe and Australia. Both trials administered once-monthly intravitreal doses of 2 mg aflibercept for 5 months followed by either aflibercept 2 mg every 4 weeks (2Q4) or aflibercept 2 mg every 8 weeks (2Q8) with laser photocoagulation.
- 3.2 The primary outcome in the trials was the mean change from baseline to 52 weeks in best corrected visual acuity (BCVA), based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score, in eyes with diabetic macular oedema (DMO) involving the centre of the macula, for aflibercept compared with laser photocoagulation. The results showed a statistically significant improvement in BCVA with aflibercept compared with laser photocoagulation in both VISTA and VIVID. The mean treatment difference for aflibercept compared with laser in the 2Q8 group of VISTA was 12.19 (97.5% confidence interval [CI] 9.35 to 15.04) and in VIVID 9.05 (97.5% CI 6.35 to 11.76).
- 3.3 The secondary outcomes of the trials included: the proportion of patients gaining 10 or more ETDRS letters and 15 or more ETDRS letters from baseline to week 52; the mean change in central retinal thickness (CRT) from baseline to week 52, as assessed on ocular coherence tomography; vision-related quality of life (assessed by the National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25]); and quality of life (assessed by the EuroQoL-5 dimension health questionnaire [EQ-5D]). The results

showed a statistically significant improvement for outcomes in both trials in people having aflibercept compared with laser. For the NEI-VFQ-25, the VISTA trial showed a statistically significant advantage with aflibercept 2Q4 (but not with aflibercept 2Q8) on the Near Activities subscale compared with laser.

- 3.4 The company carried out subgroup analyses of the secondary endpoints, including for baseline CRT (less than 400 micrometres or 400 micrometres or more) and previous cataract surgery (presence of pseudophakic lens). The results of these analyses were submitted as academic in confidence.
- 3.5 The company completed further analyses on efficacy outcomes, which included losing 5 or more, 10 or more and 15 or more ETDRS letters from baseline. The results at week 52 in the 2Q4 and 2Q8 groups in both trials showed a smaller proportion of patients in the aflibercept group losing 5 or more, 10 or more and 15 or more ETDRS letters compared with the laser group.
- 3.6 The company undertook a meta-analysis of the results from the VISTA and VIVID trials for some outcomes using both fixed and random effects models. The meta-analysis comparisons were made exclusively between aflibercept 2Q8 and laser because this is the dose that has a marketing authorisation in the UK. The results from the meta-analysis showed a greater gain in mean BCVA from baseline to 12 months with aflibercept, when compared with laser. The results also indicated that a higher proportion of patients treated with aflibercept achieved a gain of 10 or more ETDRS letters or 15 or more ETDRS letters, from baseline to 12 months, when compared with laser photocoagulation, and that a lower proportion of patients treated with aflibercept lost 15 or more ETDRS letters or 10 or more ETDRS letters, from baseline to 12 months, when compared with laser treatment. All of these results were statistically significant.
- 3.7 The company collected EQ-5D health-related quality-of-life data during the pivotal trials at baseline, week 24 and week 52. A regression analysis was done to estimate the relationship between BCVA (in both eyes) and quality of life. Patients completed the EQ-5D questionnaires and the

quality-of-life estimates were based on a general population tariff. The mean total change score from baseline to 52 weeks in VIVID, the European arm of the study, was provided by the company as academic in confidence in the submission and therefore cannot be presented.

- 3.8 The company presented the safety data from the VISTA and VIVID trials, which showed that aflibercept had a favourable safety profile at 2 years in people with DMO.
- 3.9 The company did a systematic review to identify studies for inclusion in the network meta-analysis of aflibercept 2Q8 with ranibizumab. The company used the pooled estimates from the meta-analyses for aflibercept 2Q8 with laser. The indirect comparisons showed statistically significant improvement in the BCVA mean change from baseline in favour of anti-vascular endothelial growth factor (VEGF) treatments (both aflibercept and ranibizumab) compared with laser. Results of the network meta-analysis showed a statistically significant improvement in visual acuity as measured by BCVA mean change from baseline and loss of 10 or more ETDRS letters for aflibercept 2Q8 compared with ranibizumab. There was no significant difference between aflibercept and ranibizumab for alternative visual acuity outcomes (gain of 15 or more ETDRS letters, loss of 15 or more ETDRS letters and gain of 10 or more ETDRS letters) or safety outcomes. An indirect comparison with the pivotal MEAD study for dexamethasone was not possible because there was no common comparator. The company stated that a comparison of aflibercept with fluocinolone acetonide was not possible because there was no common comparator for an indirect analysis.

Cost effectiveness

Company's original submission

- 3.10 The company provided a bilateral vision, state transition Markov model in which each eye was in 1 of 8 possible health states. The 2 worst health states, HS7 and HS8, represented blindness. The baseline age of patients in the model was 63 years and the proportion of women patients was 42.1%. These values were based on the population enrolled in VIVID

and VISTA. The proportion of fellow eye involvement at baseline (46.5%) was drawn from expert opinion rather than the VIVID and VISTA trial data. The starting vision health state distributions for the study eye and the fellow eye were estimated from the baseline characteristics of participants in the integrated VIVID and VISTA trial analyses.

- 3.11 The company used the results of the VISTA and VIVID trials to inform laser efficacy in the model (BCVA based on gaining or losing 10 or 15 ETDRS letters). Aflibercept and ranibizumab efficacy in the model were based on the probabilities of gaining or losing 10 or 15 ETDRS letters, which were estimated by applying the relative risks calculated as part of the network meta-analysis. Dexamethasone efficacy was based on the probability of gaining 10 ETDRS letters, which was estimated by applying the relative risks from the indirect comparison of aflibercept with dexamethasone using the PLACID study. For the comparison of aflibercept with fluocinolone acetonide, rates of improvement were taken directly from the FAME trial (that compared fluocinolone acetonide with sham fluocinolone acetonide); rates of worsening were assumed to be the same as those of laser from the VISTA and VIVID trials.
- 3.12 The health states in the company's economic model were defined by vision in both eyes and therefore health state utilities (and hence quality-adjusted life years [QALYs]) account for the better seeing eye and the worse seeing eye. This approach needed 36 utility values to account for every possible combination of the better seeing eye and worse seeing eye. The company used 4 sources of health-related quality-of-life data in its cost-effectiveness analyses. For its base-case analyses, the company used utility values from Czoski-Murray et al. (2009). The company stated that they had used these values because they had been accepted by the Appraisal Committee during the appraisal of other technologies for DMO (NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#) and [fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy](#)). The company also used utility values from the EQ-5D data collected in the pivotal trials (submitted as academic in confidence), and Brown (1999) and Brown (2000) in the sensitivity analyses (see tables 1 and 2). The company's submission provided details of an ordinary least squares analysis of the

pooled VIVID and VISTA EQ-5D data. This regresses quality of life on the BCVA logarithms of the better seeing eye and of the worse seeing eye. The utility values from Czoski-Murray et al. (2009), Brown (1999) and Brown (2000) apply to the BCVA in both eyes (bilateral), therefore the company applied a 30% utility decrement to the better seeing eye to estimate the utility of each corresponding health state in the worse seeing eye (resulting in a proportional decrement of 23%). The company assumed a constant utility in each health state meaning utility changes were only in relation to BCVA and not the duration spent in the health state. For adverse events, disutilities were applied for cataract, endophthalmitis, retinal detachment, glaucoma, vitreous haemorrhage and raised intraocular pressure.

Table 1 BCVA quality of life: values for the better seeing eye

	Czoski-Murray et al. (2009)	Brown (1999)	Brown (2000)
HS1	0.856	0.839	0.890
HS2	0.764	0.839	0.890
HS3	0.690	0.783	0.810
HS4	0.617	0.783	0.690
HS5	0.543	0.732	0.558
HS6	0.469	0.681	0.545
HS7	0.396	0.630	0.520
HS8	0.263	0.579	0.460

Table 2 BCVA quality of life: values for the worse seeing eye

	Czoski-Murray et al. (2009)	Brown (1999)	Brown (2000)
HS1	0.856	0.839	0.890
HS2	0.835	0.839	0.890
HS3	0.818	0.826	0.872
HS4	0.801	0.826	0.844

HS5	0.784	0.814	0.813
HS6	0.767	0.803	0.810
HS7	0.750	0.791	0.805
HS8	0.720	0.779	0.791

- 3.13 In the company's cost-effectiveness analyses the unit cost of treatment with aflibercept was modelled using the confidential patient access scheme. Adverse event costs were taken from NHS reference costs. In addition, an average annual cost of blindness of £6448 was obtained from the literature, and updated for inflation. This cost was applied to both eyes in the HS7 or HS8 health states. The company modelled 8 aflibercept treatments in the first year, in line with the marketing authorisation and assumed all treatment visits would double as monitoring visits. People in the ranibizumab arm were assumed to receive 7.93 ranibizumab treatments in the first year along with 12 monitoring visits. The company acknowledged that the summary of product characteristics for ranibizumab had recently changed to reduce the number of monitoring visits needed in the first year. This change was not included in the model because it was not considered by the company to be established practice in England.
- 3.14 The company's base-case incremental cost-effectiveness ratios (ICERs) reported that aflibercept (all ICERs reported in the company's analysis used the confidential patient access scheme price for aflibercept) dominated (is more effective and less costly than) laser and ranibizumab (when the list price of ranibizumab was used). The company explored the effect of different patient access scheme discounts on the list price of ranibizumab. The results showed that the ICER for aflibercept remained under £20,000 per QALY gained up to a ranibizumab price discount of 70%.
- 3.15 The company's scenario analyses compared aflibercept with dexamethasone and fluocinolone acetonide. These analyses showed that aflibercept (using the confidential patient access scheme price) dominated both dexamethasone and fluocinolone acetonide. The company undertook exploratory analyses comparing aflibercept with fluocinolone acetonide in a subgroup of patients with pseudophakic

lenses. In this comparison, probabilities of gaining 10 and 15 ETDRS letters were obtained from the pseudophakic subgroup in VIVID and VISTA and from the FAME trial (gaining 15 or more ETDRS letters for fluocinolone acetonide). The company presented the results of the exploratory analyses using both the list price of fluocinolone acetonide and applying various discounts (0% to 100%). Aflibercept continued to dominate fluocinolone acetonide in all of the subgroup analyses.

- 3.16 The company performed a scenario analysis for a subgroup of patients with CRT of 400 micrometres or more, using the probabilities of gaining and losing ETDRS letters for the subgroup of patients in the VIVID and VISTA trials. The results showed that aflibercept dominated both laser and ranibizumab.

Evidence Review Group comments on the company's original submission

- 3.17 The ERG commented that the main entry criterion for VIVID and VISTA was a CRT of 1 micrometre in the central retina (defined as clinically significant macular oedema). The ERG stated that this is usually determined by ocular coherence tomography, but the company did not mention its use in the submission. Therefore, at entry, patients may or may not have fulfilled the standard definition of clinically significant macular oedema. However, clinically significant macular oedema was used as the re-treatment criterion for laser photocoagulation therapy. The ERG stated that it could be argued that the initial laser treatment was not based on the presence of clinically significant macular oedema, whereas the re-treatments were; the rationale for this was unclear to the ERG. The ERG noted that it was also not specified whether fluorescein angiography was done before laser treatment to guide the laser (as recommended by the ETDRS).
- 3.18 The ERG noted that patients in VIVID had a significantly higher mean CRT than patients in VISTA for the laser and aflibercept 2Q8 groups. The ERG commented that this may be important because there is evidence that the clinical effectiveness of anti-VEGF treatment for DMO varies according to baseline CRT measurements. The ERG noted that more eyes

in VISTA had previous anti-VEGF treatment than eyes in VIVID (42.9% compared with 8.9%, respectively). The ERG also noted that about half of the patients in VISTA had also had previous laser photocoagulation treatment in the study eye. The ERG commented that the mean HbA1c across VISTA and VIVID was 7.6 to 7.9, which is lower than most people seen in clinical practice in England, who often have HbA1c levels over 8 or 9. Therefore, it is possible that aflibercept may be less effective in clinical practice than in the results of the pivotal trials. The ERG considered that the integrated analysis was not appropriate because the VISTA and VIVID trials differed significantly in the proportion of patients who had previous anti-VEGF treatment and in the mean CRT.

3.19 The ERG identified aspects of the company's original base-case model that involved errors in the data analysis and also identified parameter values, which it preferred. These are listed below:

- Revising the number of aflibercept injections in the first year from 8.0 to 8.50. The ERG noted that the dosing specified in the summary of product characteristics for aflibercept suggested that it could be applied every 4 weeks, which would result in a mean number of 8.50 injections in the first year.
- Revising the number of aflibercept injections in year 2 from 4.0 to 5.45. The ERG noted that the company had assumed an equal number of injections in the second year for ranibizumab and aflibercept. The ERG obtained the mean number of injections reported in VISTA and VIVID (5.45) and used this in its revised analysis.
- Revising the number of ranibizumab injections in the first year to 7.93. The ERG noted that the number of injections of ranibizumab may have been overestimated by the company. The ERG noted that the company combined the mean number of injections reported in the RESTORE and REVEAL trials with the median number from the DRCR.net trial. The ERG commented that it may not be appropriate to combine the values in this way.
- The number of monitoring visits for ranibizumab (12) in the first year may have been overestimated because the recently revised summary of product characteristics for ranibizumab removes the need for additional hospital monitoring visits in the first year of treatment.

- Correcting the cost of blindness in the company model and applying a discount of 3.5%. The ERG commented that the method used in the company's model to inform the cost of blindness (£6448) was overestimated because it used the annual amount monthly and it was not discounted.
 - The company used utility values from Czoski-Murray (2009) in its base-case analyses. For these values to fit the better seeing eye and worse seeing eye states separately, the company has allowed for a proportion of the better seeing eye utility impact for a given change in the health state to apply to the same change in the health state of the worse seeing eye. The ERG noted a discrepancy in the decrement applied to the worse seeing eye, which was stated as 30% in the company's submission but resulted in a proportional difference of 23%.
 - Not treating eyes in HS7 and HS8 health states (blindness) during the maintenance phase, as in the company's base case.
- 3.20 The results of the ERG's base-case analysis comparing aflibercept (using the confidential patient access scheme discount price) with laser reported an ICER of £33,921 per QALY gained (incremental QALYs 0.381; incremental costs cannot be reported because these were considered commercial in confidence).
- 3.21 The results of the ERG's base-case analysis comparing aflibercept with ranibizumab showed that aflibercept dominated ranibizumab when the list price of ranibizumab was used. The ERG presented the results over various ranibizumab patient access scheme discounts. The ICERs ranged from dominant (0% discount) to £111,215 per QALY gained (100% discount).
- 3.22 The ERG also did sensitivity analyses. The parameters that were changed included:
- exploring the use of the VIVID and VISTA EQ-5D utility data using the ordinary least squares, random effects and generalised estimating equation models
 - exploring the health-related quality-of-life values from Brown (1999) and Brown (2000)
 - excluding the REVEAL trial relative risks (trial was based on a predominantly

Asian population)

- exploring the effect of reducing the proportion of people in the model who were blind and needed residential care from 30% to 20% (that reduced the annual average cost of blindness from £7429 to £5640).

3.23 The results of the ERG sensitivity analyses for aflibercept compared with laser showed ICERs above £30,000 per QALY for all parameters with the exception of using the Brown (2000) values (ICER £29,915 per QALY gained). The results of the ERG sensitivity analyses for aflibercept compared with ranibizumab (over various patient access scheme discounts) showed ICERs that ranged from aflibercept dominating ranibizumab to ICERs of up to £1,260,695 per QALY gained (100% ranibizumab discount using the EQ-5D generalised estimating equation analysis). The ERG noted that in these analyses the choice of quality-of-life values had the biggest effect on the ICER.

3.24 The ERG did an additional cost-effectiveness analysis to examine the CRT subgroups for aflibercept compared with laser (less than 400 micrometres or 400 micrometres or more). The ERG used the company's post hoc analysis of CRT subgroups to calculate the relative risks from the VIVID and VISTA trials of aflibercept compared with laser in gaining or losing 10 or 15 ETDRS letters. The ERG used these relative risks to derive probabilities to recalculate the ICERs for the two subgroups using the ERG's base case. The results of the cost-effectiveness subgroup analysis showed the ICER for aflibercept compared with laser of £21,958 per QALY gained in the CRT 400 micrometres or more group and £49,421 per QALY gained in the CRT less than 400 micrometres group.

New evidence submitted by the company following consultation on the appraisal consultation document

3.25 The company was granted permission to provide a new cost-effectiveness analysis for the comparison of aflibercept with laser in the whole trial population. The new analysis used the ERG's original base-case analysis (see section 3.19), which was discussed by the

Committee and documented in the appraisal consultation document (ACD). The company provided new evidence (see section 3.26) and further rationale (see section 3.27) to support reinstating its original base-case assumptions for some of the parameters.

3.26 The company presented new evidence to support its view that the ERG had overestimated the number of aflibercept injections in year 1 and year 2 and underestimated the cost of a laser administration visit in its base-case analysis. The company's new evidence included:

- An online survey of 10 ophthalmologists to establish the mean number of injections and monitoring visits in each year of treatment. The results of the survey showed the average number of injections of aflibercept were 6.5 and 4.1 in years 1 and 2 respectively. The company commented that this was lower than that estimated in the VIVID and VISTA trials and supports the hypothesis that a similar number of injections should be assumed for aflibercept and ranibizumab in years 1 and 2. The results for the number of monitoring visits of aflibercept showed a mean of 5.6 in year 1 and 4.2 in year 2.
- An online survey of 34 ophthalmologists to establish the mean time taken for a laser visit compared with an intravitreal injection visit. The results of the survey showed the mean time spent with a patient for a laser visit was 23.7 minutes compared with 22.30 minutes for an intravitreal injection visit. The company commented that this supports increasing the cost of a laser administration visit to equal the cost of an intravitreal injection visit.

3.27 The company's new analysis included the following amendments to the ERG's original base-case analysis:

- Increased aflibercept injections in year 1 from 8.50 to 8.55 and decreased the injections in year 2 from 5.45 to 4.0. The company also assumed the same number of injections in year 1 and year 2 for aflibercept and ranibizumab. The company stated that the estimated number of aflibercept injections in year 1 and year 2, used in the ERG's base-case analysis, did not reflect the summary of product characteristics for aflibercept, or clinical opinion (obtained from the online survey of 10 UK ophthalmologists; see section 3.26). The company also stated that the online survey supported the assumption that a similar number of injections should be assumed for ranibizumab and aflibercept in year 1 and year 2.

- Increased cost of a laser administration from £139 to £256. The company stated that based on the results of the online survey of 34 ophthalmologists (see section 3.26), it was appropriate to assume at least a similar administration cost for injection and laser visits. The company acknowledged however, that it was aware that the actual cost varied across England.
- Increased laser monitoring visits from 4.00 to 12.00 in the first year to equal the number of laser visits in VISTA and VIVID. The company highlighted that the number of laser administrations in VIVID, VISTA and the ranibizumab trials was based on monthly monitoring visits because this was when the decision to administer an injection was undertaken.
- Used 46% instead of 85% for the rate for fellow eye involvement at baseline. The company commented that the rate of fellow eye involvement assumed at baseline and accepted by the committee in NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#) was 35%. It also commented that it was aware of several epidemiological studies that suggested the rate of clinically significant DMO is lower than any other form of DMO in the UK.
- Used an alternative mortality rate from Preis et al. (2006). The company stated that the ERG had used a mortality rate of 2.45 based on Mulnier et al. (2006), which was used in other NICE technology appraisals of treatments for eye conditions including NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#). The company commented that the Preis. et al. study was a more recent study than Mulnier. et al., but it acknowledged that both studies had strengths and limitations.
- Used patient-level data from the VIVID and VISTA trials to inform the transition probabilities for aflibercept. The company commented that the ERG had stated in its original report that the use of patient-level data would be more appropriate. The company noted that no patient-level data was available for ranibizumab.

3.28 The company's new economic analysis reduced the ICER for aflibercept (with the confidential patient access scheme applied) compared with laser in the whole trial population from £33,921 per QALY gained (see section 3.20) to £21,718 per QALY gained.

Evidence Review Group's response to the company's new evidence and analysis following consultation

- 3.29 The ERG reviewed the new evidence presented by the company for the comparison of aflibercept with laser in the whole trial population (see section 3.26) and the company's amendments to the ERG's original base case (see section 3.27).
- Decreased aflibercept injections in year 1. The ERG questioned the validity of the results from the online survey of 10 ophthalmologists, which suggested a mean of 6.5 aflibercept injections in year 1. The ERG commented that the results suggested that the ERG had either misinterpreted the summary of product characteristics for aflibercept or that the ophthalmologists surveyed anticipated a higher discontinuation rate than was observed in VIVID and VISTA. The ERG highlighted that based on the wording of the summary of product characteristics for aflibercept, calendar-month dosing would imply 8 administrations in the first year while 4-weekly dosing would imply 8.55 (that was in line with the mean number of administrations during VIVID and VISTA).
 - Decreased aflibercept injections in year 2. The ERG stated that the amendment for the number of aflibercept injections in year 2 encompasses 2 changes: i) equivalence of treatment numbers with ranibizumab and ii) applying the number of ranibizumab injections from the RESTORE extension study rather than the higher number of aflibercept injections from the VIVID and VISTA trials. The ERG commented that in its base-case analysis, the number of aflibercept and ranibizumab injections in year 2 was calculated from the mean number of injections given in VIVID and VISTA and in the RESTORE extension study. The ERG acknowledged that the number of aflibercept injections in VIVID and VISTA may be protocol driven, but stated that the clinical effectiveness evidence for aflibercept relates to the dosing frequency used in VIVID and VISTA. Therefore, the estimate for the number of injections of aflibercept from these trials should be used in the base case because of their alignment to the dosing frequency. The ERG commented that the concerns it had about the validity of the results from the 10 UK ophthalmologists for the number of aflibercept injections in year 1 also raised concerns about the reliability of the mean estimate of 4.0 aflibercept injections for the second year of the online survey. However, the ERG acknowledged that it had questioned to

what degree the dosing of aflibercept might be protocol driven in its original report, and therefore the ERG applied 4.0 aflibercept injections in year 2 within a sensitivity analyses.

- Cost of a laser administration: The ERG noted the results of the online survey of 34 ophthalmologists to establish the mean time taken for a laser visit compared with an intravitreal injection visit. The ERG accepted that it was plausible to assume the same administration cost for laser as for intravitreal injections. It noted that in the new company analysis the figure used was higher than the cost of an injection (£256). It therefore corrected this to £196 in its revised analysis.
- Mortality multiplier: The ERG-preferred mortality multiplier from Mulnier et al. (2006; a multiplier for people with diabetes compared with the general population) was combined with a mortality multiplier from Hirai et al. (2008; a mortality multiplier for people with diabetes and DMO compared with people with diabetes and without DMO). The ERG explained that if the mortality multiplier from Preis et al. (2005) was combined with the mortality multiplier from Hirai et al., it would result in a similar overall mortality rate to that used in the ERG's original base-case analysis.
- Fellow eye involvement: The ERG stated that reducing the fellow eye involvement at baseline by approximately half (from 85% to 46%) would have no overall impact on the results because the model is designed to assume only 50% of fellow eyes get treated. The ERG explored the impact on the ICER in a sensitivity analysis of a 46% fellow eye involvement with 50% on treatment and with 100% on treatment.
- Laser monitoring visits in year 1: The ERG stated that increasing the number of laser monitoring visits in year 1 from 4 to 12 was inappropriate because current professional guidance suggests no more than 4 monitoring visits per year.
- Use of patient-level trial data: The ERG noted that the use of patient-level data from VIVID and VISTA to inform the transition probabilities could improve the ICER for aflibercept compared with laser. However, because these data were not used in the company's submission, the ERG was unclear as to how it was generated and utilised in the company's model.

3.30 The ERG redid its original base-case analysis for the comparison of aflibercept with laser using an equivalent cost of a laser administration

with an intravitreal injection thereby increasing the cost of a laser administration from £139 to £194 (corrected by the ERG from £256 in the company's new evidence and analysis; see section 3.27). The results of the revised analysis showed the ICER for aflibercept (incorporating the confidential patient access scheme) compared with laser in the whole trial population reduced from £33,921 to £33,123. The ERG also provided a revised subgroup analysis for people with a CRT of less than 400 micrometres and for people with a CRT of 400 micrometres or more. The ERG's revised base cases for people with a CRT less than 400 micrometres was £48,255 per QALY gained and for people with a CRT of 400 micrometres or more was £21,442 per QALY gained.

3.31 The ERG conducted a sensitivity analysis on the parameters that it considered important to further explore for the comparison of aflibercept with laser in the whole trial population (section 3.29). The assumptions explored were:

- equivalent cost for laser and intravitreal injection visits
- 4.0 aflibercept injections in year 2
- 2.3 aflibercept injections in year 3
- 46% fellow eye involvement at baseline with 100% on treatment
- 46% fellow eye involvement at baseline with 50% on treatment
- using the EQ-5D random effects quality-of-life data from VIVID and VISTA
- using the EQ-5D general estimating equation quality-of-life data from VIVID and VISTA.

3.32 The results of the ERG's sensitivity analysis for aflibercept (incorporating the confidential patient access scheme) compared with laser in the whole trial population showed the ICER ranged from £30,793 for 4.0 aflibercept injections in year 2 to £114,463 per QALY gained using the trial EQ-5D trial data.

3.33 The ERG conducted the sensitivity analysis for the 2 subgroups: the CRT less than 400 micrometres and the CRT 400 micrometres or more. The results of the sensitivity analyses in the CRT less than 400 micrometres

group showed the ICERs ranged from £44,883 per QALY gained for 4.0 aflibercept injections in year 2 to £185,829 per QALY gained using the EQ-5D trial data. In the CRT 400 micrometres or more group, the ICERs ranged from £19,925 per QALY gained for 4.0 aflibercept injections in year 2 to £78,268 per QALY gained using the EQ-5D trial data.

3.34 Full details of all the evidence are [available](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of aflibercept, having considered evidence on the nature of diabetic macular oedema (DMO) and the value placed on the benefits of aflibercept by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.
- 4.2 The Committee heard from the clinical and patient experts about the impact of living with visual impairment caused by DMO. It heard from patient experts that sight loss from DMO can result in significant life changes including: loss of physical independence and reduced capacity for self-care (including diabetes management); loss of financial independence (because of forced early retirement, loss of income and dependence on benefits); reduced emotional wellbeing (depression); and loss of driving licence. In addition people are more at risk of falls and accidents. The Committee heard from the clinical experts that DMO causes central vision loss, but people may also have other eye comorbidities affecting peripheral vision that can lead to total vision loss. The clinical experts noted that the earlier DMO is treated, the better the prognosis for the person. The Committee heard that people having anti-vascular endothelial growth factor (VEGF) treatments find fixed treatment appointments helpful, particularly those people who are in employment or who have childcare or elderly caring responsibilities. The Committee concluded that loss of vision caused by DMO impairs quality of life and additional treatment options would be of value to people with DMO and their carers.
- 4.3 The Committee considered the clinical pathway for people with DMO and the comparators for this appraisal. It noted that the final scope issued by NICE included laser photocoagulation, ranibizumab, bevacizumab, dexamethasone and fluocinolone acetonide. The Committee heard from clinical experts that the use of laser photocoagulation had declined in recent years because of the retinal scarring associated with the procedure and the uptake of new treatments for DMO (intravitreal anti-VEGF treatments and corticosteroids). The clinical experts advised

that in current clinical practice people with DMO and a central retinal thickness (CRT) of 400 micrometres or more would have regular ranibizumab intravitreal injections (NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#)). In patients who have a CRT of less than 400 micrometres, bevacizumab (outside of its marketing authorisation) and laser photocoagulation may be used. The Committee noted comments received during consultation from a comparator company that people with a CRT of less than 400 micrometres may have no access to first-line therapy because laser is no longer routinely used. It also heard from the clinical experts that some clinicians may adopt a 'watch-and-wait' approach until CRT reaches 400 micrometres before starting ranibizumab intravitreal injections. The Committee noted comments received during consultation from a comparator company that 'watch-and-wait' is not a standard of care for patients with DMO because it may impact future treatment outcomes. The Committee heard from the clinical experts that corticosteroids (dexamethasone or fluocinolone acetonide) are only given to people whose disease has not adequately responded to anti-VEGF treatments; therefore they concluded that corticosteroids were not relevant comparators in this appraisal. The Committee concluded that although bevacizumab is used, it had seen insufficient evidence on bevacizumab to make any robust comparisons with aflibercept needed for a cost-effectiveness analysis. The Committee further concluded that ranibizumab and laser were appropriate comparators in this appraisal.

Clinical effectiveness

- 4.4 The Committee considered the clinical-effectiveness data from the VISTA and VIVID trials that compared laser therapy with aflibercept (2 mg intravitreal injections every 4 weeks or every 8 weeks after 5 initial monthly doses). The Committee discussed the concerns of the Evidence Review Group (ERG) about the generalisability of the results to clinical practice in England. The Committee heard that the trials included patients whose mean HbA1c was lower than generally found in clinical practice in England, meaning that people in a clinical setting may not respond to treatment as well as reported in the clinical trials. The Committee heard from the clinical experts that HbA1c values do not

normally affect the prognosis or treatment options for people with DMO. Cardiovascular markers, for example hypertension, have a bigger impact on the disease. The Committee concluded that overall the trials were generalisable to clinical practice in England.

- 4.5 The Committee considered the results of the VISTA and VIVID trials, which reported that aflibercept significantly improved visual acuity compared with laser for the primary outcome of mean change in best corrected visual acuity (BCVA). The results of the secondary outcomes showed that aflibercept was better than laser in all outcomes apart from in the NEI-VFQ-25 quality-of-life scores in VISTA 2Q8. The Committee concluded that aflibercept was better than laser based on the results presented in the trials. The Committee considered the ERG's subgroup analysis for the clinical effectiveness of aflibercept compared with laser in the CRT 'less than 400 micrometres' group (see [section 3.24](#)) and the company's and ERG's subgroup analyses for '400 micrometres or more' group (see [sections 3.4](#) and [3.24](#) respectively). The ERG used the post-hoc analysis of the VISTA and VIVID trials, presented by the company, to establish the relative risk of aflibercept compared with laser for the gains and losses in visual acuity for the 2 subgroups. The Committee heard from the ERG that results of the analysis were uncertain because it broke the randomisation, was based on small patient numbers (n=78 in the less than 400 micrometres group and n=208 in the 400 micrometres or more group) and used inappropriately pooled data from the VISTA and VIVID trials. The subgroup analyses showed a statistically significant improvement in visual acuity gains and prevention of visual acuity losses with aflibercept compared with laser in patients with a CRT of 400 micrometres or more. In the CRT less than 400 micrometres group, aflibercept had no significant improvement over laser in all but 1 of the visual acuity outcomes. The Committee noted the comments received during consultation from the comparator companies about the recently published results from the Protocol T study. It was aware that the study compared the relative efficacy and safety of aflibercept with bevacizumab and ranibizumab and that it provided some evidence for the relative effectiveness of aflibercept compared with bevacizumab and with ranibizumab in people with a CRT less than 400 micrometres. The Committee also noted the comments from one of the comparator companies and heard from the ERG that the evidence

from the trial for the comparison of aflibercept with ranibizumab was not relevant for this appraisal because the ranibizumab treatment arm was dosed at 0.3 mg pro re nata (PRN), which is not consistent with the dose specified in the summary of product characteristics for ranibizumab (0.5 mg PRN). The Committee acknowledged the limitations of the subgroup analysis on CRT from the Protocol T study and agreed that the results could not be considered in its decision-making. The Committee also acknowledged the limitations of the subgroup analysis on CRT from the VIVID and VISTA trials but concluded that it was the only clinical data provided on the effectiveness of aflibercept in this group and that the results could be considered for decision-making.

- 4.6 The Committee considered the evidence from the network meta-analysis submitted by the company. It noted that the results indicated a statistically significant difference between aflibercept and ranibizumab for mean change in BCVA but no significant differences in alternative visual acuity outcomes (for example gain of 15 or more Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, gain of 10 or more ETDRS letters, or safety). The Committee considered comments received in consultation by a comparator manufacturer regarding the network meta-analysis. It noted a comment that the network meta-analysis provided by the company was misleading because it did not include all the relevant trials for aflibercept (the Da Vinci trial) and ranibizumab (READ-2 or RESOLVE trials). The Committee was further aware from the ERG that another network meta-analysis comparing aflibercept with ranibizumab was identified (Haig et al. 2014), which included the Da Vinci, READ-2 and RESOLVE trials. However 3 of the trials included in the analysis were unpublished. The Committee heard from the clinical experts that because aflibercept and ranibizumab are the same class of drug they would be expected to have similar clinical efficacy. They also noted that DMO in some people may respond better to either aflibercept or ranibizumab but it is not possible to predict in advance the most effective treatment. The Committee concluded that aflibercept is likely to have similar clinical effectiveness to ranibizumab, based on the results of the network meta-analysis and clinical expert opinion.
- 4.7 The Committee considered the safety profile of aflibercept. The Committee noted the clinical experts' agreement that, based on clinical

practice and the results of the trials, aflibercept is well tolerated. The Committee accepted that there were no major safety concerns associated with aflibercept.

Cost effectiveness

- 4.8 The Committee considered the economic model submitted by the company and the ERG critique. The Committee noted that the company model was well structured and accounted for vision loss in both the better seeing eye and worse seeing eye. The Committee concluded that the company model was acceptable for assessing the cost effectiveness of aflibercept.
- 4.9 The Committee considered the cost of blindness used in the model. The Committee heard from the ERG that the annual cost of blindness had been applied monthly and had not been discounted (see [section 3.19](#)), but that this had been corrected in the original ERG base-case analysis, which the Committee concluded was appropriate.
- 4.10 The Committee considered the utility values used in the model. The Committee noted that the EQ-5D trial data could be used in the base case because it reflects the NICE reference case, but the Committee was aware that the directly measured EQ-5D values may underestimate the effect of ophthalmic conditions on health-related quality of life and the impact of improvement in BCVA. It considered that the literature-sourced values from Czoski-Murray et al. (2009) were not ideal because the values apply only to the bilateral BCVA, which meant that the company had to use an adjustment factor to calculate the utility values of the worse seeing eye. The Committee acknowledged the company's reason for using Czoski-Murray et al. (2009) utility values in its submission (that is, consistency with other NICE technology eye appraisals). It also acknowledged that sensitivity analyses using the utility values from Brown (1999) and Brown (2000) were included. It concluded that the Czoski-Murray et al. utility values, although not ideal, were an acceptable basis for its decision-making.
- 4.11 The Committee considered the cost-effectiveness analysis and incremental cost-effectiveness ratios (ICERs) for aflibercept compared

with laser for the whole trial population. It noted that aflibercept dominated (was less costly and more effective than) laser in the company's original base case and continued to dominate laser in all of the company's original sensitivity analyses. However, it noted that in the ERG's original base-case analysis, when the cost of blindness error was corrected the incremental costs increased from –£2440 (cost saving) to £12,900 and the ICER calculated by the ERG was £33,900 per quality-adjusted life year (QALY) gained ([section 3.20](#)). The Committee considered the company's new evidence and revised cost-effectiveness analyses provided after consultation on the appraisal consultation document for this comparison ([section 3.25–3.28](#)). The Committee noted that the revised company ICER for aflibercept compared with laser in the whole trial population was £21,700 per QALY gained. The Committee considered each of the company's changes to the economic model (see [section 3.27](#)) and the ERG's critique of the amendments (see [sections 3.29–3.33](#)) in turn (see [sections 4.12–4.17](#)).

- 4.12 The Committee considered the company's rationale for decreasing the number of aflibercept injections in year 2 from 5.45 to 4.00 (see [sections 3.26–3.27](#)) and the ERG's critique (see [section 3.29](#)). The Committee acknowledged that the summary of product characteristics for aflibercept and ranibizumab states a reduced dosing interval after the first 12 months, and agreed that there is uncertainty around the average number of aflibercept injections that a person would receive after the first 12 months. Given that there is no robust clinical data for estimating the average number of aflibercept injections in year 2, the Committee concluded that the economic modelling of treatment should be based on trial data, and that a sensitivity analysis that included an equalisation of the number of injections of aflibercept and ranibizumab in year 2 was an acceptable basis for its decision-making.
- 4.13 The Committee considered the company's rationale (see [sections 3.26–3.27](#)) and the ERG's critique (see [section 3.30](#)) for increasing the cost of a laser administration from £139 to £194. The Committee concluded that it was appropriate to have an equal cost for both a laser and intravitreal injection administration and agreed to increase the cost of laser administration from £139 to £194.

- 4.14 The Committee considered the company's rationale (see [section 3.27](#)) and the ERG's critique (see [section 3.29](#)) for increasing laser monitoring visits in the model from 4 to 12 in year 1. The Committee was also aware that 12 monitoring visits per year was not consistent with professional guidance. The Committee was aware of the importance of modelling according to trial protocol when considering treatment and that it was not necessary when considering monitoring (because trials have to collect regular data). The Committee concluded that it was not appropriate to increase the number of monitoring visits for laser in year 1 in the economic model.
- 4.15 The Committee considered the company's rationale (see [section 3.27](#)) and the ERG's critique (see [section 3.30](#)) for decreasing the fellow eye involvement at baseline from 85% to 46%. The Committee noted that the company's proposed amendment, in which the Committee was given to assume that all of the 46% of people would be treated, was very similar to the actual value used in the ERG's original base case and would have little impact on the ICER. The Committee concluded that it was not necessary to decrease the rate of fellow eye involvement.
- 4.16 The Committee considered the company's rationale (see [section 3.27](#)) and the ERG's critique (see [section 3.29](#)) for using the Preis et al. (2005) mortality multiplier instead of the ERG's preferred multiplier from Mulnier et al. (2006). The Committee agreed that using a mortality rate from Preis et al. rather than from Mulnier et al. would have little impact on the ICER because it would be combined with the mortality multiplier from Hirai et al. (2008). The Committee concluded that it was not necessary to include the mortality multiplier from Preis et al. in the cost-effectiveness analysis.
- 4.17 Using patient-level data from the VIVID and VISTA trials to inform the transition probabilities in the economic model: The Committee considered the company's rationale (see [section 3.27](#)) and the ERG's critique (see [section 3.29](#)) for the use of patient-level data. The Committee accepted that the patient-level data may improve the ICER for aflibercept compared with laser but was concerned that it had not been critiqued by the ERG. Furthermore the Committee heard that the company had not used these data for any analysis of the patient group

with a CRT of less than 400 micrometres. The Committee concluded that it was not necessary to include individual patient data from the VISTA and VIVID trials instead of the relative risks from the network meta-analysis in the cost-effectiveness analysis.

- 4.18 The Committee then considered the revised base-case ICER for aflibercept compared with laser in the whole trial population that incorporated the Committee's preferred assumption of an increased cost of laser administration. The Committee noted that the ICER was £33,100 per QALY gained. The Committee also considered the sensitivity analysis applying 4.0 aflibercept injections in year 2 and noted that the ICER was £30,800 per QALY gained. The Committee agreed that it was appropriate to use the company's revised base-case analysis and the resulting ICER for aflibercept compared with laser of £33,100 per QALY gained. However it was aware from the clinical experts that in clinical practice the choice of treatment depends on the CRT and so it agreed that it should consider separately the cost effectiveness of aflibercept compared with laser in people with a CRT of less than 400 micrometres and in people with a CRT of 400 micrometres or more.
- 4.19 The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with a CRT of less than 400 micrometres (for whom ranibizumab is not recommended; NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#)). The ICER for the whole trial population had suggested that aflibercept compared with laser in this group was not a cost-effective use of NHS resources. The Committee noted that the ICER for the less than 400 micrometres CRT subgroup was £49,400 per QALY gained for the comparison of aflibercept with laser. The Committee noted that the company had not submitted any new evidence for this subgroup in its response to consultation on the appraisal consultation document. It considered the revised ICER using the increased cost of laser administration, which was £48,300 per QALY gained (see [section 3.30](#)). The Committee heard from the clinical experts that the use of laser as the standard of care for treatment of DMO is declining. In this subgroup, clinicians sometimes prefer to use bevacizumab outside its marketing authorisation (when available) or adopt a watch-and-wait strategy until CRT increases and the person becomes eligible for treatment with

ranibizumab. The Committee noted that it had not been presented with evidence on the cost effectiveness of aflibercept compared with bevacizumab or with a 'watch-and-wait' strategy. The Committee concluded that, based on its consideration of all the evidence (including no evidence of its cost effectiveness against other treatment strategies), aflibercept is not a cost-effective use of NHS resources compared with laser treatment for people with a CRT of less than 400 micrometres and is therefore not recommended.

- 4.20 The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with CRT 400 micrometres or more. The ICER for people with a CRT of 400 micrometres or more was £22,000 per QALY gained. The Committee noted that the company had not submitted any new evidence for this group in response to consultation. It considered the revised ICER by the ERG using the increased cost of laser administration, which was £21,400 per QALY gained (see [section 3.30](#)). However, the Committee was aware that the main comparator for this population was ranibizumab, but no comparison with ranibizumab was included in the cost-effectiveness evidence for the CRT subgroups (section 4.21).
- 4.21 The Committee considered the cost-effectiveness analysis and ICERs for aflibercept compared with ranibizumab for the whole trial population. The Committee was aware of the actual discount agreed in the patient access scheme for ranibizumab (this is commercial in confidence and therefore cannot be reported). It noted that the range of analyses (0%–100% discount from the list price) undertaken by the company and the ERG included the discount agreed in the patient access scheme for ranibizumab. The Committee noted that when the exact discount agreed in the patient access scheme for ranibizumab was taken into account, the ICERs for aflibercept compared with ranibizumab from the company's base-case analysis and from the ERG's analysis were within the range normally considered to be a cost-effective use of NHS resources (up to £20,000 per QALY gained). However, the Committee noted that ranibizumab is currently only recommended by NICE for people with DMO whose CRT is 400 micrometres or more (NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#)). The Committee considered that the whole population analysis

taken together with clinical expert testimony justified a conclusion that, for people with a CRT of 400 micrometres or more where ranibizumab is the comparator treatment, aflibercept is a cost-effective use of NHS resources for treating people with DMO.

- 4.22 The Committee considered the potential cost effectiveness of sequential treatment with anti-VEGF agents. The Committee was not presented with any cost-effectiveness data on the sequential use of anti-VEGF treatments. The Committee raised concerns that potentially multiple treatments of ranibizumab could be followed by multiple treatments of aflibercept (if the person's disease does not adequately respond to ranibizumab). The Committee noted that because an increase in costs of treatment in this circumstance would not be matched by a similar gain in QALYs it is unlikely that sequential treatment with ranibizumab followed by aflibercept would be cost effective. The clinical experts explained that because anti-VEGF treatments (NICE's technology appraisal guidance on [ranibizumab for treating diabetic macular oedema](#)) have only been available for a limited amount of time, there is no established best practice on the optimal conditions for switching anti-VEGF treatments. The Committee concluded that, in the absence of evidence, no recommendations could be made on the cost effectiveness of sequential treatment with anti-VEGFs.
- 4.23 The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It noted the clinical expert views that aflibercept was a useful addition to the anti-VEGF products available.
- 4.24 The Committee considered whether it should take into account the consequences of Pharmaceutical Price Regulation System (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising aflibercept. The Appraisal Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of aflibercept. It therefore concluded that the PPRS

payment mechanism was irrelevant for the consideration of cost effectiveness of aflibercept.

Summary of Appraisal Committee's key conclusions

TA346	Appraisal title: Aflibercept for treating diabetic macular oedema	Section
Key conclusion		

<p>Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema (DMO) only if the eye has a central retinal thickness (CRT) of 400 micrometres or more at the start of treatment and the company provides aflibercept with the discount agreed in the patient access scheme.</p>	<p>1.1 4.5 4.19 4.20</p>
<p>The Committee considered the subgroup analyses for the clinical effectiveness of aflibercept compared with laser in the CRT 'less than' and 'greater than' 400 micrometres groups from the VIVID and VISTA trials. In patients with a CRT greater than 400 micrometres, aflibercept significantly improved visual acuity gains and prevented visual acuity losses compared with laser. In the CRT less than 400 micrometres group, aflibercept had no significant improvement over laser in visual acuity outcomes.</p>	<p>4.6 4.21</p>
<p>The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with a CRT of less than 400 micrometres (for whom ranibizumab is not recommended; NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema). The ICER for the whole trial population had suggested that aflibercept compared with laser in this group was not a cost-effective use of NHS resources. The Committee noted that the ICER for the less than 400 micrometres CRT subgroup was £49,400 per QALY gained for the comparison of aflibercept with laser. The Committee noted that the company had not submitted any new evidence for this subgroup in its response to consultation on the appraisal consultation document. It considered the revised ICER using the increased cost of laser administration, which was £48,300 per QALY gained.</p>	
<p>The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with CRT 400 micrometres or more. The ICER for people with a CRT of 400 micrometres or more was £22,000 per QALY gained. The Committee noted that the company had not submitted any new evidence for this group in response to consultation. It considered the revised ICER by the ERG using the increased cost of laser administration, which was £21,400 per QALY gained. However, the Committee was aware that the main comparator for this population was ranibizumab, but no comparison with ranibizumab was included in the cost-effectiveness evidence for the CRT subgroups.</p>	
<p>The Committee considered the clinical-effectiveness evidence of aflibercept compared with ranibizumab. The evidence showed that there is no significant difference in clinical effectiveness. Ranibizumab is currently</p>	

<p>recommended for people with DMO whose CRT is greater than 400 micrometres (NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema). The Committee considered the cost-effectiveness evidence for the comparison of aflibercept with ranibizumab (including the ranibizumab patient access scheme discount). The ICER showed aflibercept was cost effective compared with ranibizumab (ICER less than £20,000 per QALY gained). The Committee considered that the whole population analysis taken together with clinical expert testimony justified a conclusion that, for people with a CRT of 400 micrometres and more where ranibizumab is the comparator treatment, aflibercept is a cost-effective use of NHS resources for treating people with DMO.</p>		
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The clinical experts advised that in current clinical practice people with DMO and a CRT of 400 micrometres or more would have regular ranibizumab intravitreal injections (NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema). In patients who have a CRT of less than 400 micrometres, bevacizumab (outside of its marketing authorisation) and laser photocoagulation may be used. The Committee noted comments received during consultation from a comparator company that people with a CRT of less than 400 micrometres may have no access to first-line therapy because laser is no longer routinely used. It also heard from the clinical experts that some clinicians may adopt a 'watch-and-wait' approach until CRT reaches 400 micrometres before starting ranibizumab intravitreal injections.</p>	<p>4.3</p>
<p>The technology</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?	The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It noted the clinical expert views that aflibercept was a useful addition to the anti-VEGF products available.	4.23
What is the position of the treatment in the pathway of care for the condition?	Aflibercept has a UK marketing authorisation for the treatment of adults with DMO.	2.1
Adverse reactions	The Committee noted the clinical experts' agreement that, based on clinical practice and the results of the trials, aflibercept is well tolerated. The Committee accepted that there were no major safety concerns associated with aflibercept.	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The main sources of evidence presented in the company's submission came from 2 ongoing phase-III trials: VIVID and VISTA. Both trials are double-blind, randomised (1:1:1) active-controlled superiority studies. VISTA (n=466) is carried out at 54 sites in the USA. VIVID (n=406) is carried out at 73 sites across Japan, Europe and Australia.</p> <p>Both trials administered once-monthly intravitreal doses of 2 mg aflibercept for 5 months followed by either aflibercept 2 mg every 4 weeks (2Q4) or aflibercept 2 mg every 8 weeks (2Q8) with laser photocoagulation.</p>	3.1

Relevance to general clinical practice in the NHS	The Committee heard that the trials included patients whose mean HbA1c was lower than generally found in clinical practice in England, meaning that people in a clinical setting may not respond to treatment as well as reported in the clinical trials. The Committee heard from the clinical experts that HbA1c values do not normally affect the prognosis or treatment options for people with DMO. Cardiovascular markers, for example hypertension, have a bigger impact on the disease. The Committee concluded that overall the trials were generalisable to clinical practice in England.	4.4
Uncertainties generated by the evidence	The Committee heard from the Evidence Review Group (ERG) that results of the analysis were uncertain because it broke the randomisation, was based on small patient numbers (n=78 in the less than 400 micrometres group and n=208 in the 400 micrometres or more group) and used inappropriately pooled data from the VISTA and VIVID trials.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The clinical experts advised that in current clinical practice, people with DMO and a CRT of 400 micrometres or more would have regular ranibizumab intravitreal injections. In patients with a CRT of less than 400 micrometres, laser photocoagulation is a relevant treatment option but clinicians may alternatively adopt a 'watch-and-wait' approach until CRT reaches 400 micrometres or give bevacizumab outside of its marketing authorisation.	4.3
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that aflibercept was better than laser based on the results presented in the trials. The Committee concluded that aflibercept is likely to have similar clinical effectiveness to ranibizumab, based on the results of the network meta-analysis and clinical expert opinion.	4.5 4.6
Evidence for cost effectiveness		

<p>Availability and nature of evidence</p>	<p>The Committee noted that the company model was well structured and accounted for vision loss in both the better seeing eye and worse seeing eye. The Committee concluded that the company model was acceptable for assessing the cost effectiveness of aflibercept.</p>	<p>4.8</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee heard from the ERG that the annual cost of blindness had been applied monthly and had not been discounted in the company's model.</p> <p>The Committee acknowledged that the summary of product characteristics for aflibercept and ranibizumab states a reduced dosing interval after the first 12 months, and agreed that there is uncertainty around the average number of aflibercept injections that a person would receive after the first 12 months. Given that there is no robust clinical data for estimating the average number of aflibercept injections in year 2, the Committee concluded that the economic modelling of treatment should be based on trial data, and that a sensitivity analysis that included an equalisation of the number of injections of aflibercept and ranibizumab in year 2 was an acceptable basis for its decision-making.</p> <p>The Committee considered the company's rationale and the ERG's critique for increasing the cost of a laser administration from £139 to £194. The Committee concluded that it was appropriate to have an equal cost for both a laser and intravitreal injection administration and agreed to increase the cost of laser administration.</p>	<p>4.9 4.12 3.26–3.27; 3.30; 4.13</p>

<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>The ERG considered the literature-sourced values from Czoski-Murray et al. (2009) were not ideal because the values apply only to the bilateral best corrected visual acuity, which meant that the company had to use an adjustment factor to calculate the utility values of the worse seeing eye. The Committee acknowledged the company's reason for using Czoski-Murray et al. (2009) utility values in its submission (that is, consistency with other NICE technology eye appraisals). It also acknowledged that sensitivity analyses using the utility values from Brown (1999) and Brown (2000) were included. It concluded that the Czoski-Murray et al. utility values, although not ideal, were an acceptable basis for its decision-making.</p>	<p>4.10</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee heard from clinical experts that in clinical practice the choice of treatment depends on the CRT and so it considered separately the cost effectiveness of aflibercept compared with laser in people with a CRT of less than 400 micrometres and in people with a CRT of 400 micrometres or more.</p>	<p>4.18</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The results of the ERG sensitivity analyses over various ranibizumab discounts showed ICERs up to £1,260,695 per QALY gained (100% ranibizumab discount using the EQ-5D generalised estimating equation analysis). The ERG noted that in these analyses the choice of quality-of-life values had the biggest effect on the ICER.</p>	<p>3.23</p>

Most likely cost-effectiveness estimate (given as an ICER)	<p>For aflibercept compared with ranibizumab in the whole trial population, the ICER is within the range considered to be a cost-effective use of NHS resources (below £20,000 per QALY gained).</p> <p>The Committee then considered the revised base-case ICER for aflibercept compared with laser in the whole trial population that incorporated the Committee's preferred assumption of an increased cost of laser administration. The Committee noted that the ICER was £33,100 per QALY gained.</p> <p>The Committee noted that the ICER for the less than 400 micrometres CRT subgroup was £49,400 per QALY gained for the comparison of aflibercept with laser. It considered the revised ICER using the increased cost of laser administration, which was £48,300 per QALY gained.</p> <p>The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with CRT 400 micrometres or more. The ICER for people with a CRT of 400 micrometres or more was £22,000 per QALY gained. It considered the revised ICER by the ERG using the increased cost of laser administration, which was £21,400 per QALY gained (see section 3.30).</p>	4.21 4.18 4.19 4.20
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme is in place for aflibercept. Ranibizumab also has a patient access scheme in place.	2.4
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No issues relating to equality considerations were raised in the submission, or in the Committee meeting.	

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 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has diabetic macular oedema and the doctor responsible for their care thinks that aflibercept is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Bayer Pharma have agreed that aflibercept will be available to the NHS with a patient access scheme, which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company 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 Bayer Pharma, lesley.gilmour@bayer.com.
- 5.5 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 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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 2015

7 Appraisal Committee members, guideline representatives and NICE project team

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 Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

David Chandler

Lay Member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Professor Wasim Hanif

Professor in Diabetes and Endocrinology, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Emily Lam

Lay Member

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Suzanne Martin

Reader in Health Sciences

Dr Iain Miller

Founder and Chief Executive Officer, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Professor 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

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

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.

Victoria Kelly

Technical Lead

Nicola Hay/Eleanor Donegan

Technical Advisers

Lori Farrar

Project Manager

8 Sources of evidence considered by the Committee

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

- Fielding S, Cummins E, Cruickshank M et al. Aflibercept for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen HTA Group, 2014

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, the ERG report and the appraisal consultation document. Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bayer Pharma

II. Professional/expert and patient/carer groups:

- Diabetes UK
- Fight for Sight
- Royal National Institute of Blind People (RNIB)
- Royal College of Ophthalmologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- NHS Stafford & Surrounds Clinical Commissioning Group

- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Alimera Sciences
- Novartis Pharmaceuticals
- Roche Products

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on aflibercept for treating diabetic macular oedema by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Ian Pearce, Consultant Ophthalmologist, nominated by Bayer Pharma – clinical expert
- Sobha Sivaprasad, Consultant Ophthalmologist, nominated by Royal College of Ophthalmologists, endorsed by RNIB, Macular Society and Diabetes UK – clinical expert
- Clara Eaglen, Policy and Campaigns Manager, nominated by RNIB – patient expert
- Clive Worrall, nominated by RNIB – patient expert

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

- Bayer Pharma

About this guidance

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

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

It has been incorporated into the NICE pathway on [eye conditions](#) along with other related guidance and products.

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

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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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