

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Aflibercept for treating diabetic macular
oedema**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using aflibercept in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using aflibercept in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 11th March 2015

Second Appraisal Committee meeting: 24th March 2015

Details of membership of the Appraisal Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

- 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 which 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.
- 2.4 The list price of aflibercept is £816.00 per vial (excluding VAT; British national formulary [BNF] edition January 2015). 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 8) considered evidence submitted by the company on aflibercept and a review of this submission by the Evidence Review Group (ERG; section 9).

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 US. 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 5 one-monthly intravitreal doses of 2 mg aflibercept followed by either

aflibercept 2 mg every 4 weeks or (2Q4) 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 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 all 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. No statistically significant differences were observed in either trial for the NEI-VFQ-25 Distance Activities subscale.
- 3.4 The company carried out subgroup analyses of the secondary endpoints, including for baseline CRT (less than 400 or greater

than 400 micrometres) 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 and dexamethasone. The company used the pooled estimates from the meta-analyses for aflibercept 2Q8 with laser (VIVID and VISTA trials). For the comparison of ranibizumab with laser, the RESTORE and REVEAL trials were used. For dexamethasone compared with laser, the PLACID trial was used. The indirect comparisons showed statistically significant improvement in the BCVA mean change from baseline in favour of anti-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). The results for aflibercept compared with dexamethasone showed a statistically significant improvement with a 'gain of 10 or more ETDRS letters'. 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

- 3.10 The company provided a bilateral vision, state transition Markov model in which each eye was in 1 of 8 possible health states (HS). 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 (which 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 QALYs) account for the best seeing eye and the worst seeing eye.

This approach needed 36 utility values to account for every

possible combination of the best seeing eye and worst 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 technology appraisal 274, [Ranibizumab](#) for treating diabetic macular oedema and NICE technology appraisal guidance 301, [Fluocinolone acetonide](#) intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy [rapid review of technology appraisal guidance 271]). 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 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 best seeing eye and of the worst 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 best seeing eye to estimate the utility of each corresponding health state in the worst 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 best 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 worst seeing eye

	Czoski-Murray et al. (2009)	Brown (1999)	Brown (2000)
HS1	0.8559	0.8390	0.8900
HS2	0.8346	0.8390	0.8900
HS3	0.8177	0.8261	0.8715
HS4	0.8007	0.8261	0.8438
HS5	0.7837	0.8143	0.8134
HS6	0.7667	0.8025	0.8104
HS7	0.7497	0.7908	0.8046
HS8	0.7192	0.7790	0.7908

3.13 In the company’s cost-effectiveness analyses the unit cost of treatment with aflibercept was modelled using the confidential patient access scheme acquisition cost of aflibercept. 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 assumed that people would receive 8 aflibercept treatments in the first year and all treatment visits would double as monitoring visits in line with the marketing authorisation. 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 dominated (is more effective and less costly) 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 £30,000 per QALY gained up to a ranibizumab price discount of 80%.
- 3.15 The company's scenario analyses compared aflibercept with dexamethasone and fluocinolone acetonide. These analyses showed that aflibercept 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 greater than 400 micrometres, 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

- 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 those 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 base-case model that involved errors in data analysis, parameter values and methodology. These are listed below:

- The number of ranibizumab injections in the first year (7.93) 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 DCRC.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.
- The ERG commented that the data 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 best seeing eye (BSE) and worst seeing eye (WSE) states separately, the company has allowed for a proportion of the BSE utility impact for a given change in the health state to apply to the same change in the health state of the WSE. The ERG noted a discrepancy in the decrement applied to the worst seeing eye

which was stated as 30% in the company submission but resulted in a proportional difference of 23%.

3.20 The ERG built an exploratory base-case analysis which corrected errors identified during its critique of the model. The amendments included:

- revising the number of aflibercept injections to 8.50, 5.45 and 3.00 in years 1, 2 and 3
- revising the number of ranibizumab injections to 7.43, 4.00 and 3.00 in years 1, 2 and 3
- not treating eyes in HS7 and HS8 health states (blindness) during the maintenance phase, as in the company base case
- applying a discount of 3.5% to the costs of blindness.

3.21 The results of the ERG's base-case analysis comparing aflibercept with laser reported an ICER of £33,921 per QALY gained (incremental QALYs 0.381, incremental costs cannot be reported as these were considered commercial in confidence).

3.22 The results of the ERG's base-case analysis comparing aflibercept with ranibizumab showed that aflibercept dominated ranibizumab. 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).

3.23 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).
- exploring the effect of reducing the proportion of people in the model who were blind and needed residential care from 30% to 20% (which reduced the annual average cost of blindness from £7429 to £5640).

3.24 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 this analysis the choice of quality life values had the biggest effect on the ICER.

3.25 The ERG did an additional cost effectiveness analysis to examine the CRT subgroups for aflibercept compared with laser (less than 400 micrometres or greater than 400 micrometres). 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 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 greater than 400 micrometres group and £49,421 per QALY gained in the CRT less than 400 micrometre group.

3.26 Full details of all the evidence are in the [committee papers](#).

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 co-morbidities affecting peripheral vision which can lead to total vision loss. The clinical experts noted that the earlier DMO is treated the better the prognosis for the patient. The Committee heard that patients having anti-VEGF treatments find fixed treatment appointments helpful, particularly those patients 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 patients 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 greater than 400 micrometres would have regular ranibizumab intravitreal injections ([NICE technology appraisal guidance 274](#)). In patients who have a CRT of less than 400 micrometres, laser photocoagulation is a comparator and bevacizumab may be given outside of its marketing authorisation. In addition clinicians may adopt a 'watch-and-wait' approach until CRT reaches 400 micrometres before starting ranibizumab intravitreal injections. The Committee heard from the clinical experts that corticosteroids (dexamethasone or fluocinolone acetonide) are only given to patients 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 of intravitreal injections every 4 weeks or every 8 weeks after

5 initial monthly doses). The Committee discussed the Evidence Review Group (ERG)'s concerns 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 patients 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 analyses for the clinical effectiveness of aflibercept compared with laser in the CRT 'less than' and 'greater than' 400 micrometre groups. 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 analyses 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 greater than 400 micrometre 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 greater than 400 micrometres. In the CRT less than 400 micrometres group, aflibercept had no significant improvement over laser in visual acuity outcomes. The Committee acknowledged the limitations of the sub-group analysis on CRT but concluded that it was the only clinical data provided on the effectiveness of aflibercept in this group and concluded 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 that reported no statistically significant difference between aflibercept and ranibizumab in alternative visual acuity outcomes (for example 'gain of 15 or more ETDRS letters', 'gain of 10 or more ETDRS letters' or safety). 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 concluded 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 best seeing eye and worst 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 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 worst seeing eye. The Committee acknowledged the rationale of the company for using Czoski-Murray et al. (2009) utility values in its submission (that is consistency with other 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 utility values, although not ideal, were an acceptable basis for its decision making.

- 4.11 The Committee considered the cost-effectiveness analysis and ICERs from the base-case results of the company model and the ERG analysis for aflibercept compared with laser for the whole trial population. It noted that aflibercept dominated (less costly and more effective) laser in the company base-case and continued to dominate laser in all company sensitivity analyses. However, it noted that in the ERG's base-case analysis, when the cost of blindness error was corrected the incremental costs increased from -£2438 (cost saving) to £12,931 and the ICER calculated by the ERG was £33,921 per QALY gained. The Committee heard 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 CRT greater than 400 micrometres.
- 4.12 The Committee considered the ICERs presented by the ERG for the CRT less than 400 micrometre subgroup of patients treated with aflibercept compared with laser (for whom ranibizumab is not recommended by NICE). The ICER for the trial population had suggested that aflibercept compared with laser in this group was not a cost-effective use of NHS resources. This was reinforced by the less than 400 micrometre CRT sub-group ICER of £49,421 per QALY gained for the comparison of aflibercept with laser. The Committee heard from the clinical experts that the use of laser is declining as the standard of care for treatment of DMO. 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 the evidence presented, (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.

4.13 The Committee considered the ICERs presented by the ERG for aflibercept compared with laser in the subgroup CRT greater than 400 micrometres. The ICER for people with a CRT of greater than 400 micrometres was £21,958 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 sub-groups (paragraph 4.14).

4.14 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 ICER 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 more than 400 micrometres ([NICE technology appraisal guidance TA274](#)) The

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

- 4.15 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 isn't adequately responding to ranibizumab). The Committee noted that because an increase in compounded costs of treatment 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 technology appraisal guidance 274](#)) 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-VEGF's.
- 4.16 The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It agreed that aflibercept could be considered a slight advance compared with ranibizumab because of the less frequent administration of treatment and the reduced need for monitoring.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Aflibercept for treating diabetic macular oedema	Section
Key conclusion		
<p>Aflibercept 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.</p> <p>The Committee considered the subgroup analyses for the clinical effectiveness of aflibercept compared with laser in the central retinal thickness (CRT) 'less than' and 'greater than' 400 micrometre 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>In the less than 400 micrometre CRT sub-group the ICER was £49,421 per QALY gained. The Committee concluded that in this group aflibercept was not a cost effective use of NHS resources. The Committee considered the cost effectiveness analysis for the subgroup CRT greater than 400 micrometres (ICER £21,958 per QALY gained). The Committee noted the clinical expert testimony that ranibizumab is the main comparator in this group.</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.</p> <p>Ranibizumab is currently recommended for people with DMO whose</p>		<p>1.1, 4.5-6, 4.11-15</p>

<p>CRT is greater than 400 micrometres (NICE technology appraisal guidance 274). 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 more than 400 micrometres, where ranibizumab is the comparator treatment, aflibercept was 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, the people with DMO and a central retinal thickness (CRT) of greater than 400 micrometres would have regular ranibizumab intravitreal injections. In patients who have 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 bevacizumab is given outside its marketing authorisation. The Committee heard from the clinical experts that corticosteroids are only given to patients whose disease has not adequately responded to anti-VEGF treatments.</p>	<p>4.3</p>

The technology		
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 agreed that aflibercept could be considered a slight advance compared with ranibizumab because of the less frequent administration of treatment and the reduced need for monitoring.	4.16
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 concluded that there were no major safety concerns associated with aflibercept.	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The main source 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 a carried out at 54 sites in the US. VIVID (n=406) is carried out at 73 sites across	3.1

	<p>Japan, Europe and Australia.</p> <p>Both trials administered 5 one-monthly intravitreal doses of 2 mg aflibercept followed by either aflibercept 2 mg every 4 weeks or (2Q4) aflibercept 2 mg every 8 weeks (2Q8) with laser photocoagulation.</p>	
<p>Relevance to general clinical practice in the NHS</p>	<p>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 patients 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.</p>	<p>4.4</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee considered the ERG's concerns that the results of the post-hoc subgroup analysis of CRT were uncertain because it broke randomisation, were based on small patient and used inappropriately pooled data from the VISTA and VIVID trials.</p>	<p>4.5</p>

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The clinical experts advised that in current clinical practice, the people with DMO and a central retinal thickness (CRT) of greater than 400 micrometres would have regular ranibizumab intravitreal injections. In patients who have 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.</p> <p>The subgroup analyses showed that in patients with a CRT greater than 400 micrometres aflibercept significantly improved visual acuity gains and prevented visual acuity losses compared with laser.</p> <p>In the CRT less than 400 micrometres group, aflibercept had no significant improvement over laser in visual acuity outcomes.</p>	<p>4.3, 4.5</p>
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<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>On the basis of the trials, the Committee concluded aflibercept significantly improved visual acuity compared with laser for the primary outcome of mean change in best corrected visual acuity (BCVA)</p> <p>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.</p>	<p>4.5,4.6</p>
<p>Evidence for cost effectiveness</p>		
<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 best seeing eye and worst 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 model.</p>	<p>4.9</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 BCVA, which meant that the company had to use an adjustment factor to calculate the utility values of the worst seeing eye. The Committee acknowledged the rationale of the company for using Czoski-Murray et al. (2009) utility values in its submission (that is consistency with other 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 utility values, although not ideal, were an acceptable basis for its decision making</p>	<p>4.10</p>
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<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 CRT greater than 400 micrometres. The ICER for people with a CRT of greater than 400 micrometres was £21,958 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 sub-groups</p>	<p>4.13</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>3.24</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For aflibercept compared with ranibizumab in the intention-to-treat population, the ICER is within the range considered to be a cost-effective use of NHS resources (below £30,000 per QALY gained).</p> <p>For aflibercept compared with laser in the intention-to-treat population, the ICER calculated by the ERG was £33,921 per QALY gained. The Committee concluded that, if laser was the comparator treatment, aflibercept was not a cost-effective use of NHS resources for treating people with DMO.</p> <p>For aflibercept compared with laser in the greater than 400 micrometre subgroup, the ICER is £21,958.</p> <p>For aflibercept compared with laser in the less than 400 micrometre subgroup, the ICER is £49,421.</p>	<p>4.11-15</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>A patient access scheme is in place for aflibercept. Ranibizumab also has a patient access scheme in place</p>	<p>2.4, 4.14</p>
<p>End-of-life considerations</p>	<p>Not applicable.</p>	

<p>Equalities considerations and social value judgements</p>	<p>No issues relating to equality considerations were raised in the submission, or in the Committee meeting.</p>	
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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 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.

5.3 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 [NICE to add details at time of publication]

5.4 NICE has developed tools [link to [www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this

guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy \(rapid review of technology appraisal guidance 271\). NICE technology appraisal guidance 301. 2013.](#)
- [Ranibizumab for treating diabetic macular oedema \(rapid review of technology appraisal guidance 237\). NICE technology appraisal guidance 274. 2013.](#)

Under development

- Dexamethasone intravitreal implant for treating diabetic macular oedema. NICE technology appraisal guidance, publication expected 2015.

7 Proposed date for review of guidance

- 7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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 Stevens
Chair, Appraisal Committee
February 2015

8 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
National Institute for Health and Care Excellence

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 & CEO, 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 & 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 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:

- 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 (ACD). 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 CCG
- 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 are 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

E. 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