NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion

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, 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see 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 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 NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 29 June 2016

Second appraisal committee meeting: 13 July 2016

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Aflibercept is recommended as an option for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion, only if:

- laser photocoagulation has not been beneficial or laser photocoagulation is not suitable because of the extent of macular haemorrhage and
- the company provides aflibercept with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with aflibercept was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Aflibercept solution for injection (Eylea, Bayer) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein. It has a marketing authorisation in the UK for treating 'visual impairment due to macular oedema secondary to retinal vein occlusion (branch or central)'. Aflibercept is administered by intravitreal injection.

2.2 The summary of product characteristics states that the most frequently reported adverse reactions associated with using aflibercept are conjunctival haemorrhaging, reduction in visual acuity, eye pain, cataract, intraocular pressure increasing, vitreous detachment and vitreous floaters. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Aflibercept is administered as a single 2 mg intravitreal injection. Each vial contains 4 mg of aflibercept in 0.1 ml, providing a single dose of 0.05 ml containing 2 mg of aflibercept. The list price of aflibercept is £816 for 1 vial (excluding VAT; British National Formulary, accessed May 2016). 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 Evidence

3.1 The appraisal committee (section 7) considered evidence submitted by Bayer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of aflibercept, having considered evidence on the nature of visual impairment caused by macular oedema after branch retinal vein occlusion 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 considered the nature of visual impairment and how it affects the everyday life of patients. The committee understood from clinical experts that people with macular oedema after branch retinal vein occlusion experience different severities of visual impairment. It noted that in some people the condition can resolve without intervention, but for others, particularly where diagnosis is delayed, visual outcomes can be much worse. The committee heard from patient experts that loss of visual

acuity can have a significant effect on a person's independence and severely affects their ability to undertake daily activities. The committee heard that laser photocoagulation (an alternative treatment, see section 4.4) can be painful and take longer to provide a gain in visual acuity. It understood that having an injection in the eye can cause apprehension and pain, but that patients consider the improvement in visual acuity to be worth it. The committee concluded that the loss of visual acuity can have a severe effect on quality of life and that patients would welcome additional options to treat visual impairment caused by macular oedema after branch retinal vein occlusion.

4.3 The committee considered the treatments for visual impairment caused by macular oedema after branch retinal vein occlusion currently used in NHS clinical practice. It recalled the NICE technology appraisal of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion, in which ranibizumab was compared with laser photocoagulation. It noted that laser photocoagulation was the principal treatment option, and ranibizumab was recommended where laser photocoagulation treatment was inappropriate due to the extent of macular haemorrhage. The committee heard from clinical experts in the appraisal of aflibercept in branch retinal vein occlusion that treatment options reflected this guidance. It heard that there are a substantial number of people for whom laser photocoagulation could be considered inappropriate. The committee noted that bevacizumab, unlicensed in eye conditions, is also in use in some centres in the UK. The committee noted that treatment choice depended on the severity of visual impairment, the extent of macular haemorrhaging and patient preference. It heard that in people with mild macular oedema, the condition would be observed to allow for spontaneous improvement. If some visual loss has already occurred, laser photocoagulation may be used if macular haemorrhaging isn't extensive. The committee understood that if macular haemorrhaging is extensive, laser photo coagulation is not a suitable treatment option and

instead, intravitreal injections of anti-VEGF treatments (bevacizumab, ranibizumab) or a corticosteroid (dexamethasone) implant are used. The committee concluded that monitoring the condition, laser photocoagulation, anti-VEGF treatments and corticosteroid treatment are all used for treating visual impairment caused by macular oedema after branch retinal vein occlusion.

4.4 The committee considered the comparators for aflibercept in the final scope of this appraisal. It noted bevacizumab intravitreal injection anti-VEGF treatment (ranibizumab) and corticosteroid treatment (dexamethasone) are all relevant comparators and treatment options for macular oedema after branch retinal vein occlusion (see section 4.2). The committee questioned the clinical experts on bevacizumab's relevance as a comparator and noted that it is available as a treatment option in current clinical practice. The committee recognised the consideration of bevacizumab as a comparator in the NICE technology appraisal of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. It also noted the statement from the NICE board discussing bevacizumab. The committee concluded that although bevacizumab is a potentially comparator, no evidence had been presented so it could not assess the clinical or cost effectiveness of aflibercept compared with bevacizumab.

Clinical effectiveness

4.5 The committee considered the evidence presented by the company on the clinical effectiveness of aflibercept. It was aware that the company's evidence comprised 3 separate comparisons:

- Aflibercept after laser photocoagulation compared with ranibizumab after laser photocoagulation (when appropriate).
- Aflibercept after laser photocoagulation compared with dexamethasone after laser photocoagulation (when appropriate).

- Aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation (when appropriate).

The committed understood that the company's comparisons presented sequences of treatment with aflibercept. The first 2 propose aflibercept where dexamethasone and ranibizumab are currently used. The committee was mindful of the third sequence, in which aflibercept was used in patients with untreated visual impairment, aflibercept was present in both treatment arms (that is, aflibercept was compared with itself at different stages of the treatment pathway).

4.6 The committee examined the clinical effectiveness evidence for aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation, using evidence provided by the company from the randomised control trial VIBRANT. The committee noted that 74% of patients in the laser photocoagulation group went on to have aflibercept. The committee acknowledged that at 52 weeks, a significantly higher proportion of patients gained 15 or more letters in the aflibercept in patients with untreated visual impairment group compared with the aflibercept after laser coagulation group (52.7% and 41.1% respectively, $p<0.05$). The committee noted that the company used the last observation carried forward approach to impute missing data for patients that dropped out of the trial. Any rebound among patients who dropped out would be unobservable, as would longer-term gains from the gradual effects of laser photocoagulation. It agreed that this approach could overestimate the clinical efficacy of aflibercept but was unable to quantify the exact effect. Therefore, the committee concluded that aflibercept could be more clinically effective in patients with untreated visual impairment (caused by macular oedema after branch retinal vein occlusion) than when given after laser photocoagulation.

4.7 The committee considered the clinical effectiveness of aflibercept after laser photocoagulation compared with dexamethasone after laser

photocoagulation and with ranibizumab after laser photocoagulation. The committee was aware that no direct trial evidence was available for these comparisons, and it discussed the results of the network meta-analysis presented by the company. It noted that both the mean and median odds ratios of gaining 15 or more letters favoured aflibercept when compared with dexamethasone (mean 0.39, median 0.34 [crl: 0.12, 0.96]). However, when compared with ranibizumab, the median odds ratio favoured aflibercept, whereas the mean odds ratio favoured ranibizumab (median 0.93, mean 1.04 [crl:0.38, 2.31]). The committee considered that in all cases, the credible intervals around the mean and median estimates were wide, and that the point estimates should therefore be interpreted with caution. The committee understood that in the comparison with ranibizumab, the results were not statistically significant and that either ranibizumab or aflibercept could be considered marginally more clinically effective dependent on the assumptions made. The clinical experts informed the committee that ranibizumab and aflibercept are considered equivalent in terms of clinical efficacy and tolerability. Considering both the results of the network meta-analysis and the clinical experts' evidence, the committee concluded that aflibercept is clinically more effective than dexamethasone and equivalent to ranibizumab in terms of visual acuity in branch retinal vein occlusion.

Cost effectiveness

4.8 The committee considered the cost-effectiveness evidence submitted by the company. The committee noted that the incremental cost-effectiveness ratio (ICER) of aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation was £15,365 per quality-adjusted life year (QALY) gained (including the patient access scheme). Costs and QALYs are confidential so cannot be presented here. The committee acknowledged the ERG's concerns with some of the assumptions used in the company's base case:

- Patients may need anti-vascular endothelial growth factor (VEGF) treatment for more than 5 years, whereas the company's base case stopped anti-VEGF treatment after 5 years.
- The probabilities used to estimate the likelihood of a person gaining or losing visual acuity were not derived directly from patient data.
- Quality-of-life data were taken from Czoski-Murray (2009) although more appropriate data were available.
- Quality-of-life estimation for the worst-seeing eye relative to best-seeing eye may not be as high as 30% as used in the model.

The committee considered each issue in turn, as detailed below.

4.9 The committee considered the long-term anti-VEGF dosing requirements. It noted that in the company's base case, anti-VEGF treatment was stopped after 5 years. The committee heard evidence from the ERG that studies have shown a need for continued anti-VEGF beyond 5 years. It also heard from the clinical experts that around 30% of patients need ongoing anti-VEGF treatment beyond 5 years. The committee concluded that it is clinically plausible to assume that anti-VEGF treatment will continue beyond 5 years for some patients with visual impairment caused by macular oedema following branch retinal vein occlusion.

4.10 The committee considered the source of transition probabilities used in the model. It noted that the company's model assumed that the probabilities of improving or worsening visual acuity were derived by fitting a model to long-term data. The committee understood that the probabilities could instead have been derived directly from patient data and considered that there was no evidence to suggest that these data should not be used in the model. The committee concluded that using real-world data to estimate the probabilities of improving or worsening visual acuity was a preferable approach.

4.11 The committee considered the source of quality-of-life data used in the company's model. It noted that EQ-5D data were collected in the VIBRANT trial, but that the company's economic model used health state utility values from Czoski-Murray et al. (2009). By using the Czoski-Murray values, the utility for the worst health state associated with visual impairment (that is, blindness in both eyes) was 0.29. The committee noted that this is very low and implies that people would trade more than two thirds of life with very poor vision to have good vision. The committee considered alternative sources of utility data and noted from the ERG's exploratory analyses that using utilities from a study by Brown (1999) increased the ICER of aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation to £36,631 per QALY gained. It also considered the utility data taken from the VIBRANT trial, which raised the ICER to over £50,000 per QALY gained. The committee noted that trial EQ-5D estimates can be insensitive in eye disease, so considered that the utility values from the Brown study were the most plausible estimates available. The committee concluded that the utility values from Brown should be used as the source of the health state utility data in the model in its decision making.

4.12 The committee considered the company's quality-of-life estimations for the worst-seeing eye relative to those for the best-seeing eye. The company had presented a bilateral model that assumed that any change in visual acuity for the worst-seeing eye would equate to 30% of a similar change in utility for the best-seeing eye. The committee recognised that this assumption was subject to some uncertainty. It considered the empirical evidence shown by the ERG that this is likely to be an overestimate, and that quality of life is much more a function of a person's better-seeing eye. It noted that in a sensitivity analysis, the ERG had lowered the proportional impact of a change in the best-seeing eye to 15%, which resulted in a ICER for aflibercept of £33,380 per QALY

gained. It concluded that quality-of-life estimates for the worst-seeing eye relative to the best-seeing eye were likely to be lower than 30%.

4.13 The committee considered the most plausible ICER for aflibercept in patient with untreated visual impairment compared with aflibercept after laser photocoagulation, given its preferred assumptions as detailed in sections 4.9 and 4.10. It noted the ERG's exploratory base-case ICER of £28,813, in which these preferred assumptions had been incorporated. The committee further considered the preferred utility assumption as detailed in section 4.11 and 4.12, noting that in each case the ICER had increased. It also noted that the handling of loss to follow-up data in the company's model, which the ERG could not remodel, may increase the ICER even higher. Nevertheless, the committee accepted these ICERs as the basis for its decision-marking with regard to aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation. The committee concluded that the most plausible ICER would be above the range that could be considered a cost-effective use of NHS resources, and so did not recommend aflibercept in patients with untreated visual impairment (that is, before laser photocoagulation).

4.14 The committee considered the most plausible ICER for aflibercept after laser photocoagulation in which aflibercept, ranibizumab and dexamethasone were compared in an incremental cost-effectiveness analysis. It considered that this population would include both those for whom grid laser photocoagulation has not been beneficial and those for whom grid laser photocoagulation is not a suitable treatment. The committee was aware that an ICER incorporating its preferred assumptions (see sections 4.9 to 4.11) had not been presented. However, it noted that in the ERG's exploratory base case (in which the transition probability matrices were drawn from real-world data and on-going anti-VEGF treatment was assumed to continue for a total of 10 years), ranibizumab was dominated by aflibercept (that is, was both more costly

and less effective) but aflibercept compared with dexamethasone produced an ICER of around £18,500 per QALY gained. It further noted from the ERG's exploratory sensitivity analyses that when the 15% worse seeing eye assumption was included, the ICER increased to around £21,500. When the Brown (1999) utilities were incorporated (without the 15% worse seeing eye assumption), this ICER increased to around £23,500 per QALY gained. In these analyses, ranibizumab remained dominated by aflibercept. The committee was mindful of its conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab (see section 4.7), and noted that aflibercept's dominance of ranibizumab would be influenced by the results of the network meta-analysis. The committee considered the cost effectiveness of ranibizumab in the appraisal of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and considered that aflibercept and ranibizumab could be similar in terms of cost effectiveness. It therefore concluded that aflibercept should be recommended as an option for treating visual impairment caused by macular oedema after branch retinal vein occlusion in the same position as already established in NICE Technology Appraisals 229 and 283 (dexamethasone and ranibizumab respectively); that is, when treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage.

4.15 The committee considered the innovative aspects of aflibercept. It noted that the company considered it to be innovative because it has higher binding affinity for VEGF-A compared with ranibizumab, and that it inhibits a wider range of growth factors. In those respects the committee agreed with the company that it could be considered innovative. However, the committee could not identify any health-related benefits that had not already been captured in the QALY calculation. The committee concluded that there was nothing additional regarding the innovative nature of

aflibercept that needed to be taken into account for the purposes of this appraisal.

4.16 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It 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 about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Aflibercept is recommended as an option for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion, only if: • laser photocoagulation has not been beneficialor laser photocoagulation is not suitable because of the extent of macular haemorrhage and • the company provides aflibercept with the discount agreed in the patient access scheme. The committee concluded that aflibercept could be more clinically effective in patients with untreated visual impairment compared with after laser photocoagulation. It also concluded that aflibercept is more effective than dexamethasone and equivalent to ranibizumab in terms		1.1, 4.6, 4.7, 4.14

of clinical effectiveness. The committee concluded that aflibercept should be recommended as on option for treating visual impairment caused by macular oedema after branch retinal vein occlusion in the same position as already established in NICE Technology Appraisals 229 and 283 (dexamethasone and ranibizumab respectively).		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee concluded that loss of visual acuity can have a severe effect on a person's quality of life and that patients would welcome additional options to treat visual impairment caused by macular oedema after branch retinal vein occlusion.	4.2
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 concluded that there was nothing additional regarding the innovative nature of aflibercept that needed to be taken into account for the purposes of this appraisal.	4.15

What is the position of the treatment in the pathway of care for the condition?	The committee concluded that monitoring the condition, laser photocoagulation, anti-VEGF and corticosteroid treatment are all used for treating visual impairment caused by macular oedema after branch retinal vein occlusion.	4.3
Adverse reactions	Not an issue in this appraisal.	-
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee examined the clinical effectiveness evidence for aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation from the randomised control trial VIBRANT. The committee was aware that no direct trial evidence was available for the comparisons of aflibercept with ranibizumab or dexamethasone, and considers the results of a NMA.	4.6, 4.7
Relevance to general clinical practice in the NHS	Not an issue in this appraisal.	-

Uncertainties generated by the evidence	The committee heard from that the company used the last observation carried forward approach to impute missing data for patients that dropped out of the trial, which created some uncertainty in the efficacy results. The committee noted that in the network meta-analysis the credible intervals around the mean and median estimates were wide, and that the point estimates should therefore be interpreted with caution.	4.6, 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups were identified.	-

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee acknowledged that at 52 weeks, a higher proportion of patients gained 15 or more letters in the aflibercept in patients with untreated visual impairment group compared with the aflibercept after laser coagulation group (57.1% and 41.1% respectively). It concluded that aflibercept was could be more clinically effective in patients with untreated visual impairment than when given after laser photocoagulation. It noted that both the mean and median odds ratios favoured aflibercept when compared with dexamethasone (mean 0.39; median 0.34). However, when compared with ranibizumab, the median and mean odds ratios were close to 1 (median 0.93; mean 1.04).The clinical experts informed the committee that ranibizumab and aflibercept are considered clinically equivalent.	4.6, 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the company had presented a bilateral model.	4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee acknowledged the following uncertainties in the company's model: • Whether patients may need anti- VEGF treatment for more than 5 years • The probabilities used to estimate the likelihood of a person gaining or losing visual acuity were not derived directly from patient data. • Quality-of-life data were taken from Czoski-Murray (2009). • Quality-of-life estimation for the worst-seeing eye relative to best-seeing eye may not be as high as 30%.	4.8 - 4.12
Incorporation of health-related quality-of-life benefits and utility values 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?	The committee noted that the company's economic model used health state utility values from Czoski-Murray et al. (2009). It concluded that utility values from the Brown study were the most plausible estimates available should be used as the source of the health state utility data in the model.	4.11

Are there specific groups of people for whom the technology is particularly cost effective?	No subgroups were identified	-
What are the key drivers of cost effectiveness?	The committee noted that using utilities from a study by Brown increased the ICERs.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	When consider the most plausible ICER for aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation. And concluded that the ICER would be above the range that could be considered a cost-effective use of NHS resources. The committee considered aflibercept compared with dexamethasone and ranibizumab and concluded that aflibercept should be recommended as an option for treating visual impairment caused by macular oedema after branch retinal vein occlusion in the same position as dexamethasone and ranibizumab respectively. That is, when treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage.	4.13, 4.14

Additional factors taken into account		
Patient access schemes (PPRS)	Recommended only if the company provides aflibercept with the discount agree in the patient access scheme. The committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of aflibercept.	1.1, 4.16
End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	No equality issues were identified.	-

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 Department of Health and Bayer 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]

6 Proposed date for review of guidance

6.1 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.

Profession Andrew Stevens
Chair, appraisal committee
June 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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.

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.

Henry Edwards

Technical Lead(s)

Joanne Holden

Technical Adviser

Stephanie Yates

Project Manager

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