NICE National Institute for Health and Care Excellence

NICE guidance

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

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.

# Contents

# 1 Recommendations

1.1 Aflibercept is recommended as an option within its marketing authorisation for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion, only if the company provides aflibercept with the discount agreed in the patient access scheme.

# 2 The technology

## Description of the technology

2.1 Aflibercept solution for injection (Eylea, Bayer) administered by intravitreal injection. It is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein.

## Marketing authorisation

2.2 Aflibercept has a marketing authorisation in the UK for treating 'visual impairment due to macular oedema secondary to retinal vein occlusion (branch or central)'. NICE has already issued guidance on aflibercept when treating visual impairment due to macular oedema secondary to central retinal vein occlusion.

## Adverse events

2.3 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.

## Recommended dose and schedule

2.4 The recommended dose of aflibercept is 2 mg, equivalent to 50 microlitres.

## Price

2.5 The list price of aflibercept is £816 for 1 vial (excluding VAT; BNF, accessed May

2016).

2.6 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

The appraisal committee 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

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.

## Nature of the condition

4.1 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 4.3) can be painful and may 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.

## Current clinical management

4.2 The committee considered the treatments for visual impairment caused by macular oedema after branch retinal vein occlusion currently used in NHS clinical practice. 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 the NICE technology appraisal guidance on ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion only recommends ranibizumab after laser photocoagulation has failed, or when it isn't an option. Similarly, the NICE technology appraisal guidance on dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion in this indication recommends dexamethasone intravitreal implant only if laser photocoagulation has failed or is unsuitable because of extensive macular haemorrhaging. However, the committee understood that clinicians and patients prefer to use anti-vascular endothelial growth factor (VEGF) treatments such as ranibizumab instead of laser photocoagulation because it is not necessary to wait for the haemorrhaging to resolve before starting treatment. The committee concluded that monitoring the condition would be the most appropriate approach for some people, whereas for others laser photocoagulation may be a suitable initial treatment for branch retinal vein occlusion. The committee further concluded that since NICE published guidance its technology appraisal on ranibizumab and dexamethasone, clinical practice has changed and anti-VEGF and corticosteroid treatments are used in the initial treatment of visual impairment caused by macular oedema after branch retinal vein occlusion.

4.3 The committee considered the comparators for aflibercept in the final scope of this appraisal. It noted that bevacizumab, ranibizumab and dexamethasone are relevant comparators because they represent current 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 also available as a treatment option in current clinical practice. The committee recognised the consideration of bevacizumab as a comparator in the NICE technology appraisal on 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 the previous decision made in the appraisal of ranibizumab, the evidence available to the committee during this appraisal, and bevacizumab's licensing all meant that although bevacizumab could potentially be a comparator, it could not confidently assess the clinical or cost effectiveness of aflibercept compared with bevacizumab.

# Clinical effectiveness

4.4 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). That is, comparing aflibercept with ranibizumab when branch retinal vein occlusion has been treated with laser photocoagulation.
- Aflibercept after laser photocoagulation compared with dexamethasone after laser photocoagulation (when appropriate). That is, comparing aflibercept with dexamethasone when branch retinal vein occlusion has been treated with laser photocoagulation.
- Aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation (when appropriate). That is, 2 treatment sequences both containing laser and aflibercept: 1 with aflibercept first and 1 with laser first.

## Clinical trial

4.5 The committee examined the clinical-effectiveness evidence for aflibercept in patients with untreated visual impairment compared with laser photocoagulation, using evidence provided by the company from the randomised control trial VIBRANT. The committee acknowledged that at 52 weeks, a significantly higher proportion of patients gained 15 or more letters in the initial aflibercept group compared with the laser photocoagulation group (57.1% and 41.1% respectively, $p<0.05$). However, because this was not as great as the benefit observed at week 24 (52.7 and 26.7 respectively, $p<0.05$), the committee was concerned that the long-term benefit of laser photocoagulation may not have been adequately captured at the 52-week time point if this trend had been observed further. The company responded to this point, explaining that because 74% of patients in the laser arm went on to have aflibercept as a rescue treatment, the benefit in this arm at week 52 was not only because of laser photocoagulation, but also rescue aflibercept. The committee considered this to be a plausible explanation, given

the high percentage of people who had rescue aflibercept. The committee concluded that on the basis of the trial evidence, aflibercept is more clinically effective than laser photocoagulation for untreated visual impairment caused by macular oedema after branch retinal vein occlusion.

4.6 The committee went on to discuss whether there is a clinical benefit of using aflibercept before laser photocoagulation rather than after laser photocoagulation. It acknowledged that the trial was not designed to provide evidence of this. However, it recalled statements from clinical experts that anti-VEGF treatments are more beneficial than laser because treatment can be started without a period of delay, during which visual acuity could further deteriorate. Therefore, the committee considered that starting treatment with aflibercept without delay could lead to a better clinical outcome in the long term than waiting for any haemorrhaging to resolve before starting treatment with laser photocoagulation. The committee concluded that clinical experience suggests that aflibercept is more clinically effective in patients with untreated visual impairment (caused by macular oedema after branch retinal vein occlusion) when given before, rather than after, laser photocoagulation.

## Network meta-analysis

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, 95% credible interval of distribution 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, 95% credible interval of distribution 0.38, 2.31). The committee considered that in all cases, the credible intervals around the distribution of treatment effects 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. 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 likely to be equivalent to ranibizumab in terms of treating visual impairment after 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 estimated to be £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 evidence review group's (ERG's) concerns with some of the assumptions used in the company's base case:

- Patients may need anti-VEGF treatment for more than 5 years, whereas the company's base case stopped anti-VEGF treatment after 5 years.
- The number of aflibercept injections in each year is likely to be higher in practice than assumed in the company's model.
- 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 et al. (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 model assumed equal risk of developing cataracts with both aflibercept and dexamethasone.

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

## Anti-VEGF dosing after 5 years

4.9 The committee 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.

## Number of aflibercept injections in each year

4.10 The committee was aware that the company used evidence from the VIBRANT trial to inform the assumptions of aflibercept dosing in year 1, and the results of a physician survey to inform the assumptions beyond year 1. The committee noted the ERG's concern that beyond 2 years of treatment, the physicians' survey seemed to underestimate the number of aflibercept injections that would be needed each year, especially compared with the RETAIN trial (physicians' survey: year 3, 2.61 injections; year 4, 1.12 injections; year 5, 0.58 injections). The committee was aware that the ERG's revised number of injections for year 3 and beyond, 3.2 aflibercept injections per year, was a 'worst-case' scenario'. It agreed that the number of aflibercept injections was likely to be higher than estimated in the physicians' survey but was uncertain of the true dosing frequency. The committee concluded that the ERG's assumed number of aflibercept injections for year 3 and beyond was a cautious assumption; fewer injections would lower the ERG's ICER, but it would remain higher than the company's own estimate.

## Transition probabilities

4.11 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 noted that the ERG had used patient count data in its base case and concluded that using patient count data to estimate the probabilities of improving or worsening visual acuity was a preferable approach.

## Quality-of-life data

4.12 The committee considered the source of quality-of-life data and the company's approach to modelling the utility gain in the worst-seeing eye as a proportion of that in the best-seeing eye. It heard 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). It also heard that 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 noted that in the NICE technology appraisal on ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion, Czoski–Murray utility values were used for the best-seeing eye (10% of the population) and a maximum utility benefit of 0.1 QALY was applied for the worst-seeing eye (90% of the population) based on Brown (2009). The committee agreed to apply a similar utility assumption from this appraisal, specifically the maximum possible utility benefit. The committee was presented with 4 utility ranges from the ERG using different sources for the utilities (Brown and Czoski–Murray) and differing proportional impact on the worst-seeing eye (30% or 15%). The committee noted the utilities presented provided a range of maximum utility benefit from 0.062 to 0.137. The committee noted that while no 1 scenario provided a maximum quality-of-life gain of 0.1, using Czoski–Murray 15% and Brown 30% provided estimates closest to 0.1, so it agreed that these could be used as a basis for its decision making. The committee concluded that the source of the utilities was subject to some uncertainty, but the maximum utility gain in the worst-seeing eye should not exceed 0.1 QALY.

## Assumed risk of cataracts

4.13 The committee noted that in the company's model dexamethasone had been

assumed to carry the same risk of causing cataracts as aflibercept. The committee was aware that treatment with a corticosteroid such as dexamethasone has a greater risk of developing cataracts compared with an anti-VEGF treatment, such as aflibercept. The committee concluded that the modelled assumption of equal cataracts risk between dexamethasone and aflibercept is unfavourable to aflibercept. It further concluded that if a more realistic assumption had been used in the cost-effectiveness analyses, the ICER for aflibercept compared with dexamethasone would likely reduce, although it was not possible to estimate the size of the reduction.

## Aflibercept in patients with untreated branch retinal vein occlusion

4.14 The committee considered the most plausible ICER for aflibercept in patients with untreated visual impairment, given some of its preferred assumptions as detailed in sections 4.8 and 4.10. It was aware that in this comparison aflibercept was compared with itself in 2 places in the pathway: before laser photocoagulation (that is, in patients with untreated branch retinal vein occlusion) and after laser photocoagulation (see section 4.4). It noted the ERG's exploratory base-case ICER of £21,500, in which these preferred assumptions had been incorporated. The committee further considered the preferred utility assumption as detailed in section 4.11, noting that utilities of Czoski–Murray 15% or Brown 30% produce ICERs of £24,900 per QALY gained and £27,300 per QALY gained respectively. 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. It concluded that the most plausible ICER was within the range that could be considered a cost-effective use of NHS resources, and recommended aflibercept in patients with untreated visual impairment (that is, before laser photocoagulation).

## Aflibercept after laser photocoagulation

4.15 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. The committee

considered the ERG's estimated ICER which incorporated its preferred assumptions (see sections 4.8, 4.10 and 4.11). In this analysis, aflibercept dominated ranibizumab (that is, aflibercept was both less costly and more effective). The committee noted that this was based on the list price of ranibizumab (the ICER incorporating the patient access scheme for ranibizumab is commercial in confidence and cannot be reported here). The committee was mindful of its conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab (see section 4.6). It also considered the cost effectiveness of ranibizumab as assessed in the NICE technology appraisal guidance on 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. The committee turned its attention to the comparison with dexamethasone. It noted that the ERG's estimated ICER for aflibercept compared with dexamethasone that incorporated its preferred assumptions (see sections 4.8, 4.10 and 4.11) was between £33,800 per QALY gained and £37,000 per QALY gained. It was aware that these ICERs may be overestimated because of certain modelling assumptions. In particular, the committee recalled its conclusion that the risk of cataracts had been overestimated for aflibercept compared with dexamethasone. It considered that if this was corrected in the economic model, the ICER would be lower. It also recalled that the number of aflibercept injections beyond 3 years in the ERG's base case was a cautious assumption (see section 4.9), and that a less pessimistic assumption may lower the ICERs. Given these uncertainties, the committee was confident that the most plausible ICER for the comparison of aflibercept with dexamethasone would be lower. In addition, the committee reasoned that it was appropriate to make a positive recommendation for aflibercept in line with that for ranibizumab, since the evidence had been presented to support the cost effectiveness of aflibercept in this comparison. It therefore concluded that aflibercept should be recommended as an option for treating visual impairment caused by macular oedema after branch retinal vein occlusion when treatment with laser photocoagulation has not been beneficial.

# Innovation

4.16 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.

# Pharmaceutical Price Regulation Scheme 2014

4.17 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.

# 5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

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 patient has visual impairment in adults caused by macular oedema after branch retinal vein occlusion and the healthcare professional responsible for their care thinks that aflibercept is the right treatment, it should be available for use, in line with NICE's recommendations.

# 6 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

**Joanne Holden**
Technical adviser

**Stephanie Yates**
Project manager

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