NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Brolucizumab for treating wet age-related macular degeneration

1 Recommendations

1.1 Brolucizumab is recommended as an option for treating wet age-related macular degeneration in adults, only if, in the eye to be treated:

- the best-corrected visual acuity is between 6/12 and 6/96
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension and
- there is recent presumed disease progression (for example, blood vessel growth, as shown by fluorescein angiography, or recent visual acuity changes).

It is recommended only if the company provides brolucizumab according to the commercial arrangement (see section 2).

1.2 If patients and their clinicians consider brolucizumab to be one of a range of suitable treatments, including aflibercept and ranibizumab, choose the least expensive (taking into account administration costs and commercial arrangements).

1.3 Only continue brolucizumab in people who maintain an adequate response to therapy. Criteria for stopping should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy.

1.4 These recommendations are not intended to affect treatment with brolucizumab that was started in the NHS before this guidance was

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published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them.

Why the committee made these recommendations

Usual treatment for age-related macular degeneration is aflibercept and ranibizumab. Clinical trial evidence and a network meta-analysis shows that brolucizumab provides similar overall health benefits to these drugs, and is similarly safe. The total costs (including administration) of brolucizumab are the same or less than those of aflibercept and ranibizumab.

Because it has similar costs and overall health benefits to aflibercept and ranibizumab, brolucizumab is recommended as an option for treating adults with wet age-related macular degeneration in line with the previous recommendations in NICE technology appraisals guidance for aflibercept and ranibizumab.

2 Information about brolucizumab

Marketing authorisation indication

2.1 Brolucizumab (Beovu, Novartis) is indicated 'in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The price of brolucizumab is £816.00 per 120 mg/ml solution for injection in a pre-filled syringe (excluding VAT; BNF). The company has a commercial arrangement (simple discount patient access scheme). This makes brolucizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), and submissions from other stakeholders. See the committee papers full details of the evidence.

Comparators

Aflibercept and ranibizumab are appropriate comparators

3.1 NICE has already produced technology appraisal guidance on aflibercept and ranibizumab in this indication. These treatments are only recommended if all of the following circumstances apply in the eye to be treated:

- the best-corrected visual acuity (BCVA) is between 6/12 and 6/96
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes).

The committee was aware that the fast track appraisal process only permits recommendations to be made in line with the recommendations of the appraisals for the comparator treatments. So, it understood that any recommendation for brolucizumab would be constrained by these criteria. The company presented a cost-comparison case, in which it proposed that:

- the overall health benefits associated with brolucizumab are similar to or greater than those associated with aflibercept and ranibizumab and
- the total costs associated with brolucizumab are similar to or lower than those associated with aflibercept and ranibizumab.

The committee understood that aflibercept and ranibizumab are standard treatments for wet age-related macular degeneration in the NHS. So, it concluded that aflibercept and ranibizumab were appropriate comparators for this appraisal.

Bevacizumab cannot be considered as a comparator in this appraisal

3.2 The committee was aware that bevacizumab was specified as a comparator in the scope issued by NICE and considered whether the company should have included it as a comparator in its submission. It acknowledged that because bevacizumab has not been appraised by NICE for treating wet age-related macular degeneration it could not be considered as a comparator in the fast track appraisal process. So, it concluded that bevacizumab was not a relevant comparator in this appraisal.

Clinical effectiveness

Brolucizumab is non-inferior to aflibercept

3.3 The company presented the results from the HAWK and HARRIER trials, comparing the safety and effectiveness of brolucizumab (3 mg and 6 mg) with aflibercept (2 mg). HAWK and HARRIER included adults aged 50 years or more with active choroidal neovascularisation caused by age-related macular degeneration and who had not had an anti–vascular endothelial growth factor therapy. The primary outcome was change in BCVA from baseline to week 48. People in HAWK and HARRIER had brolucizumab monthly for the first 3 months then every 8 or 12 weeks, or aflibercept monthly for 3 months then every 8 weeks. The HAWK results showed from baseline to week 48, the least squares mean difference (LSMD) in change in BCVA between brolucizumab (3 mg) and aflibercept was –0.6 (95% confidence interval [CI] –2.5 to 1.3). When comparing brolucizumab (6 mg) with aflibercept, the LSMD was –0.2 (95% CI –2.1 to 1.8). The HARRIER trial results showed from baseline to week 48, the LSMD in change in BCVA between brolucizumab (6 mg) and aflibercept was –0.7 (95% CI –2.4 to 1.0). The committee agreed that because there

was not a statistically significant difference in the change in BCVA results for brolucizumab and aflibercept the treatments were likely to be similar. But, it questioned whether these results confirmed that brolucizumab could be considered non-inferior to aflibercept. The company explained that there was a pre-defined non-inferiority margin of 4 letters set by the regulator, so the results confirmed brolucizumab was non-inferior to aflibercept. The ERG agreed that the results suggested brolucizumab and aflibercept were similarly effective but questioned whether the frequency and approach to dosing used in HAWK and HARRIER was reflective of clinical practice. It highlighted that most people having treatment for wet age-related macular degeneration in clinical practice would have treatment using a flexible approach such as treat and extend (TREX), pro re nata (PRN; treatment monitored frequently and administered as need), or PRN and extend (PRNX). The committee acknowledged the ERG's concerns but agreed that the results of HAWK and HARRIER were robust. It concluded that brolucizumab is non-inferior to aflibercept.

Brolucizumab, aflibercept and ranibizumab are similarly effective

3.4 To support the HAWK and HARRIER results and estimate the relative effectiveness of brolucizumab compared with ranibizumab, the company presented the results of a network meta-analysis. The network meta-analysis assessed the relative effectiveness of brolucizumab, aflibercept and ranibizumab across 6 outcomes. The network comparing mean change in BCVA from baseline to 1 year contained 13 studies, including HAWK and HARRIER (see section 3.3). The results showed that treatment with brolucizumab (6 mg) every 8 or 12 weeks was similarly effective compared with various aflibercept (2 mg) and ranibizumab (0.5 mg) dosing regimens (every 4, 8 and 12 weeks, PRN, PRNX, and TREX). The committee concluded that the effectiveness of brolucizumab is similar to aflibercept and ranibizumab.

Adverse events with brolucizumab are likely to be similar to those with aflibercept and ranibizumab

3.5 The company explained that the number of ocular and non-ocular adverse events were balanced across brolucizumab and aflibercept treatment groups in HAWK and HARRIER (see section 3.3). It also noted that the results of the network meta-analysis (see section 3.4) showed that adverse events with brolucizumab are similar to aflibercept and ranibizumab. The committee was aware that brolucizumab's summary of product characteristics notes an increased risk of retinal vasculitis and retinal vascular occlusion. The ERG explained that because these adverse events were rare, it was not likely to affect the view that the overall impact on health of those associated with brolucizumab are similar to those of aflibercept and ranibizumab. The committee concluded that adverse events with brolucizumab are likely to be similar to aflibercept and ranibizumab.

Overall health benefits

Brolucizumab provides similar health benefits to aflibercept and ranibizumab

3.6 The committee concluded that because changes in BCVA and reports of adverse events with brolucizumab, aflibercept and ranibizumab were similar, the treatments were also likely to provide similar overall health benefits.

Resource use

The number of brolucizumab injections in years 1 and 2 should be based on the trial

3.7 The company estimated the number of brolucizumab injections in years 1 and 2 from the network meta-analysis which used pooled data from HAWK and HARRIER and accounted for differences in a random-effects model. The ERG agreed that this approach was appropriate and

incorporated the company's estimates in its preferred analysis. The committee concluded that the number of brolucizumab injections in years 1 and 2 should be based on trial data and agreed the company's approach was acceptable.

The number of comparator injections in years 1 and 2 should be based on TREX regimens

3.8 To estimate the number of injections for aflibercept and ranibizumab applied in the model in years 1 and 2, the company used a weighted average approach. This approach weighted the number of injections from different treatment regimens by the amount each regimen was proportionally used in practice. The company obtained estimates of proportions from a survey of 50 healthcare professionals who are retinal specialists. The ERG noted that most people in clinical practice followed a flexible treatment regimen such as TREX and PRN. So, it considered that the company's approach which pooled different regimens was unnecessary and presented an alternative approach which separately estimated year 1 and 2 dose frequencies for TREX and PRN regimens. The committee agreed that because TREX was the most commonly used regimen in practice, it preferred analyses based on this. It concluded that for the comparators, the number of injections in years 1 and 2 should be based on TREX regimens.

The ERG's approach to estimating the number injections in year 3 and beyond is preferred

3.9 The company assumed that the number of injections given for each treatment in year 3 and beyond would be the same as the number of injections given in year 2. It explained that in absence of longer-term data, it was difficult to assume that effectiveness would be maintained if the number of injections reduced. So, it stated that assuming the number of injections was the same as in year 2 was a reasonable and consistent approach. The ERG explained that if the number of brolucizumab injections was increased because of disease activity in HAWK and

HARRIER it could not later be decreased. It highlighted that because of this, the number of brolucizumab injections given in the trials were likely to be an overestimate of the number of injections given in clinical practice. It also highlighted that there was no available data to compare injection numbers across treatments for year 3 and beyond. So, it presented an alternative, based on analysis from NICE's technology appraisal guidance on aflibercept, where the number of injections is assumed to be the same for all treatments in year 3 and beyond. The committee agreed that the company's approach could lead to an overestimate of injection numbers. It also agreed that in the absence of longer-term data to inform estimates of injection numbers in year 3 and beyond, it was reasonable to assume it would be equivalent across treatments. It was uncertain if the year 3 injection numbers estimates from NICE's appraisal of aflibercept were accurate but agreed in the absence of more robust alternatives they were acceptable for decision making. So, it concluded it preferred the ERG's approach which assumed the same number of injections for all treatments in year 3 and beyond from NICE's appraisal of aflibercept.

Cost-comparison results

Brolucizumab can be recommended on the basis of similar health benefits and similar or lower cost

3.10 The company presented cost-comparison results for brolucizumab compared with aflibercept and ranibizumab. When taking account of the confidential commercial discounts for all treatments, it showed that the total cost associated with brolucizumab was similar or lower than aflibercept and ranibizumab (the exact results are confidential and cannot be reported here). The committee acknowledged these results but recalled that it preferred the following assumptions incorporated in the ERG's preferred analysis:

- comparator injection numbers in year 1 and 2 based on TREX regimen estimates

- injection numbers in year 3 and beyond is equivalent for all treatments and based on estimates from NICE's appraisal of aflibercept.

Taking account of these assumptions, and the confidential commercial discounts for all treatments, the total cost for brolucizumab was similar or lower than aflibercept and ranibizumab (the exact are confidential and cannot be reported here). The committee concluded that the criteria for a positive cost comparison were met, because:

- the overall health benefits of brolucizumab are similar to those of aflibercept and ranibizumab
- the total costs associated with brolucizumab are similar to or lower than those of aflibercept and ranibizumab.

The committee therefore recommended brolucizumab, in line with the previous recommendations for aflibercept and ranibizumab, as a cost-effective use of NHS resources for treating wet age-related macular degeneration in adults.

Other factors

The committee considered visual impairment as a disability when formulating its recommendations

3.11 The company noted that visual impairment resulting from wet age-related macular degeneration is recognised as a disability. So, the patient population of this appraisal is a protected group under the Equality Act of 2010. The committee took the fact that brolucizumab would be used in people with visual impairment into consideration when formulating its recommendations.

4 Implementation

4.1 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. Because brolucizumab has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

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

4.3 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 wet age-related macular degeneration and the doctor responsible for their care thinks that brolucizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
December 2020

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 A.

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.

Thomas Paling
Technical lead

Nicola Hay
Technical adviser

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