NICE National Institute for Health and Care Excellence

NICE guidance

Brolucizumab for treating diabetic macular oedema

Technology appraisal guidance
Published: 31 August 2022

www.nice.org.uk/guidance/ta820

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 Brolucizumab is recommended as an option for treating visual impairment due to diabetic macular oedema in adults, only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment
- the company provides brolucizumab according to the commercial arrangement.

1.2 If patients and their clinicians consider brolucizumab to be 1 of a range of suitable first-line treatments (including aflibercept and ranibizumab), choose the least expensive treatment. Take account of administration costs, dosage, price per dose and commercial arrangements.

1.3 These recommendations are not intended to affect treatment with brolucizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Diabetic macular oedema is usually treated first with aflibercept or ranibizumab, which are already recommended by NICE for treating diabetic macular oedema if the eye has a central retinal thickness of 400 micrometres or more when treatment starts. Brolucizumab is another treatment option that works in a similar way.

Evidence from clinical trials shows that brolucizumab is as effective as aflibercept. An indirect comparison of brolucizumab with ranibizumab also suggests similar clinical effectiveness, although this is uncertain.

A cost comparison suggests brolucizumab has similar costs and overall health benefits to aflibercept or ranibizumab. So, brolucizumab is recommended for treating diabetic macular oedema if it is used in the same population as aflibercept and ranibizumab.

2 Information about brolucizumab

Marketing authorisation indication

2.1 Brolucizumab (Beovu, Novartis) is indicated 'for the treatment of visual impairment due to diabetic macular oedema'.

Dosage in the marketing authorisation

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

Price

2.3 Brolucizumab costs £816 for 1 vial of 120 mg per 1 ml solution for injection (excluding VAT; BNF online, accessed July 2022).

2.4 The company has a commercial arrangement. 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 external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Comparators

Aflibercept and ranibizumab are appropriate comparators

3.1 Aflibercept and ranibizumab are anti-vascular endothelial growth factor (anti-VEGF) injections recommended by NICE as a first treatment for diabetic macular oedema. Brolucizumab is another anti-VEGF injection that works in a similar way to aflibercept and ranibizumab. The company proposes that brolucizumab will extend the time needed between injections compared with aflibercept and ranibizumab. The committee was aware that NICE's technology appraisal guidance 799 recommends faricimab for treating diabetic macular oedema. However, this guidance was only published shortly before the committee considered brolucizumab. The committee was also aware that NICE's technology appraisal guidance 301 recommends fluocinolone acetonide implant if the diabetic macular oedema is insufficiently responsive to available therapies. Also, NICE's technology appraisal guidance 349 recommends dexamethasone intravitreal implant if the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable. The EAG confirmed that, based on clinical expert opinion, aflibercept and ranibizumab are the standard first line treatments for diabetic macular oedema. The committee concluded that aflibercept and ranibizumab were both appropriate NICE-recommended comparators.

Clinical evidence

Evidence from 2 clinical trials, KITE and KESTREL, shows similar clinical effectiveness of brolucizumab and aflibercept

3.2 Clinical evidence for brolucizumab compared with aflibercept came from 2 clinical trials. These were KITE and KESTREL. Both were phase 3 randomised controlled trials that compared brolucizumab with aflibercept in 926 adults. In both trials, aflibercept was administered 5 times during the loading phase (once every 4 weeks), then every 8 weeks during the maintenance phase. Brolucizumab was administered 5 times during the loading phase (once every 6 weeks), then every 12 weeks during the maintenance phase (some people were reassigned to have brolucizumab every 8 weeks for the remainder of the study period, based on clinician assessment of disease activity). The primary outcome measure was the mean change in best corrected visual acuity from baseline to 1 year. The evidence suggested that both treatments were similarly effective. The EAG noted that the populations in KITE and KESTREL were broader than the population that is the focus of the cost comparison. The company also provided results from post hoc subgroup analyses of people with a central subfield thickness (considered to be clinically equivalent to central retinal thickness, commonly used in other trials for diabetic macular oedema) of 400 micrometres or more, in line with the population recommended in NICE's technology appraisal guidance on aflibercept and ranibizumab. This analysis also suggested the treatments were similar. However, the EAG noted that formal testing of non-inferiority for the primary outcome was not possible for the subgroup analysis as the studies were not powered for this. Overall, the committee considered that brolucizumab is likely to be similarly clinically effective as aflibercept.

Despite uncertainty, brolucizumab is likely to have similar clinical effectiveness as ranibizumab

3.3 The company compared brolucizumab with ranibizumab in a network meta-analysis. The primary analysis covered the broader population of patients with diabetic macular oedema, and an exploratory analysis

addressed the subgroup of patients with central subfield thickness of 400 micrometres or more at baseline. The company used the broader diabetic macular oedema population for the primary analysis because it considered it was more robust. The results of this suggest brolucizumab and ranibizumab are broadly comparable. The EAG was concerned that the primary network meta-analysis did not reflect the population in the cost comparison. The findings of the network meta-analyses were also limited by the small number of studies informing some connections. In particular there were few studies linking ranibizumab at the correct dose in the subgroup of people with central subfield thickness of 400 micrometres or more. However, clinical opinion suggests that the treatments are similarly effective. The committee concluded that, despite these significant uncertainties, there was sufficient evidence of similar clinical efficacy for brolucizumab compared with ranibizumab.

Intraocular inflammation is highlighted as a potential adverse event in the summary of product characteristics

3.4 In KITE and KESTREL the overall rate of adverse events between brolucizumab and aflibercept was similar at week 52. The EAG's clinical experts noted that there was some concern about intraocular inflammation associated with brolucizumab. This had emerged during the post-marketing surveillance of brolucizumab for use in wet age-related macular degeneration. A clinical expert noted in their statement that intraocular inflammation occurred more commonly with brolucizumab than aflibercept in KESTREL. However, they considered that retinal vascular occlusion seems to occur less frequently in diabetic macular oedema than wet age-related macular degeneration. Overall, they considered brolucizumab to have a good benefit-risk profile. The committee was aware that the summary of product characteristics for brolucizumab highlights intraocular inflammation as a potential adverse event. It notes that it can occur at any time but has been observed more frequently at the beginning of treatment. It also notes that because of this, maintenance doses of brolucizumab should not be less than 8 weeks apart. The committee acknowledged these concerns and considered it important for clinicians to bear in mind the advice in the summary of product characteristics. However, it considered that because this adverse event is uncommon, a cost-comparison analysis continued

to be appropriate. This is because averaged over the whole population, the effect on quality-adjusted life years that would be captured using a cost-utility model would be expected to be small.

Cost comparison

Brolucizumab is likely to be cost saving or have similar costs compared with aflibercept and ranibizumab

3.5 The EAG identified several issues in the company's base case model. First, because people stop brolucizumab, aflibercept and ranibizumab at different rates, the company's model had an unequal risk of bilateral diabetic macular oedema for people on different anti-VEGF treatments. The EAG preferred to equalise the risk by applying the same stopping rate to all treatment arms. Second, the company had applied pooled brolucizumab injection frequency estimates from the KITE and KESTREL studies. This concerned the EAG because people in KITE could have their treatment interval extended to 16 weeks, but the marketing authorisation only specifies extension to 12 weeks. To avoid underestimating brolucizumab injection frequency, the EAG preferred to apply unpooled data from KESTREL only. Third, the EAG were generally satisfied that the unit costs applied in the model were appropriate. But based on clinical expert advice, the EAG preferred that wide field fundus examinations be done at all monitoring visits rather than the single examination assumed in the company base case. Fourth, the company assumed brolucizumab would have lower monitoring frequency than the comparators. But the EAG's clinical experts thought it possible that people having brolucizumab would have closer monitoring in the first 6 months of treatment compared with people having aflibercept or ranibizumab. This was because they were concerned about the potentially higher risk of intraocular inflammation with brolucizumab treatment (see section 3.4). The committee considered these changes were appropriate and agreed that it was important to assess the costs of greater monitoring for brolucizumab. Using these assumptions and when taking account of the commercial arrangements for all treatments, the committee was satisfied that the total cost of brolucizumab was similar to or lower than aflibercept and ranibizumab (the exact results are confidential and

cannot be reported here). The committee agreed that choosing the least expensive option from the available treatment options at the same point in the pathway was appropriate. The committee therefore recommended brolucizumab for treating diabetic macular oedema in line with the previous recommendations for aflibercept and ranibizumab.

Other factors

There are no equality issues relevant to the recommendations

3.6 The committee did not identify any equality issues.

4 Implementation

4.1 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 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 draft guidance.

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 diabetic macular oedema 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 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.

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Accreditation