NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Benralizumab for treating severe eosinophilic asthma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using benralizumab 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.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using benralizumab 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: 1 June 2018

Second appraisal committee meeting: 19 June 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Benralizumab is not recommended, within its marketing authorisation, for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists.

1.2 This recommendation is not intended to affect treatment with benralizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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

Severe asthma is usually treated with inhaled corticosteroids plus another drug, such as a long-acting beta-agonist. These may not work well enough for eosinophilic asthma, which is a type of severe asthma that can be difficult to control. Oral corticosteroids may be needed to prevent exacerbations (asthma attacks) but they cause long-term side effects. Some people are able to have mepolizumab or reslizumab, which are similar drugs to benralizumab. These help to control the asthma, and allow the oral corticosteroids to be reduced.

Clinical trial results show that taking benralizumab plus standard treatment reduces exacerbations and the use of oral corticosteroids, compared with placebo. There are no trials directly comparing benralizumab, mepolizumab and reslizumab, and the relative clinical effectiveness of these treatments is not known. A matched-adjusted indirect comparison of benralizumab with mepolizumab did not show statistically significant differences in asthma symptoms.

The cost effectiveness of benralizumab compared with standard care was estimated in a population consisting of 2 groups: people taking

maintenance oral corticosteroids or who had 4 or more exacerbations in the past year, and people not taking maintenance oral corticosteroids who had 3 exacerbations in the past year. In this mixed population, the cost-effectiveness estimates are between £34,300 per quality-adjusted life year (QALY) gained and £39,100 per QALY gained.

For people who have had 3 exacerbations and are not taking maintenance oral corticosteroids, standard care is the only relevant comparator. The cost effectiveness of benralizumab in this group of people is not known, but it is likely to be higher than for the mixed population. This would not represent a cost-effective use of NHS resources.

For people who have had 4 or more exacerbations in the past year, or are taking maintenance oral corticosteroids, mepolizumab is an appropriate comparator. In this group of people the cost-effectiveness estimates for benralizumab, compared with standard care or mepolizumab, are higher than the range usually considered a cost-effective use of NHS resources. Benralizumab cannot be recommended for treating inadequately-controlled severe eosinophilic asthma.

2 Information about benralizumab

Marketing authorisation indication	Benralizumab (Fasenra, AstraZeneca) is indicated as 'add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.'
Dosage in the marketing authorisation	The recommended dosage is 30 mg every 4 weeks for the first 3 doses then every 8 weeks, given by subcutaneous injection using a pre-filled syringe.
Price	The list price is £1,955.0 per 30 mg pre-filled syringe (company submission). The company has agreed a patient access scheme with the Department of Health and Social Care. If benralizumab had been recommended, this scheme would provide a simple discount to the list price of benralizumab 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 would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with severe eosinophilic asthma will welcome a new treatment option that reduces the need for oral corticosteroids

3.1 Severe eosinophilic asthma that is inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists is a debilitating condition, with many distressing symptoms. Exacerbations can happen without warning, be life threatening, cause fear, and result in hospitalisation and intubation. People are often unable to work and may need help with day-to-day activities because of the symptoms. The patient expert explained that, for many people with severe eosinophilic asthma, it does not respond to standard treatment and more intensive treatments are needed to control symptoms and prevent exacerbations. The clinical

experts explained that standard treatment for inadequately controlled severe eosinophilic asthma is oral corticosteroids. NICE guidance recommends biologics such as mepolizumab and reslizumab, which the patient expert noted have been life-transforming for some people. However, there are specific eligibility criteria for these drugs and not all patients are eligible to have them. The patient expert noted that inhaled or oral corticosteroids are the main treatment for preventing exacerbations in uncontrolled asthma. When taken frequently or long-term these can cause major side effects including diabetes, glaucoma, weight gain, bone-density loss, raised blood pressure and mood swings. This has a significant impact on the lives of patients and their families, including the need for numerous additional drugs and hospital visits to monitor and treat the side effects. The patient expert noted that the potential to reduce or avoid oral corticosteroids, over and above improved control of asthma symptoms, is particularly important to patients. The committee concluded that people with severe eosinophilic asthma that is uncontrolled on standard treatment would welcome a new treatment option that reduces or avoids the use of oral corticosteroids.

Benralizumab could offer an easier method of administration compared with existing biologics

3.2 The clinical experts explained that benralizumab is given as a subcutaneous injection using a pre-filled syringe. The dosing schedule is more convenient compared with reslizumab and mepolizumab that are both given every 4 weeks, needing frequent hospital visits. The first 3 doses of benralizumab are given once every 4 weeks, and then every 8 weeks. The clinical experts considered this convenience in administration a ‘step change’. The patient expert highlighted that benralizumab would be preferred by many patients because its mode of administration and dosing schedule involves less travel and fewer visits to specialist centres. The patient expert and the clinical experts confirmed that reduction in oral corticosteroid use and its associated complications would be valuable to patients and significantly improve their quality of life.

The committee concluded that benralizumab potentially offers benefits compared with existing biologics, by reducing visits to hospital, which could be important for people with severe eosinophilic asthma.

Clinical management

Current clinical management of severe asthma

3.3 The clinical experts explained that treatment for asthma in clinical practice follows the NICE guideline on diagnosis, monitoring and chronic asthma management and the Global Initiative for Asthma 2017 guideline (which includes the use of mepolizumab, reslizumab and omalizumab). Management of uncontrolled asthma uses a step-up approach in which the dose of inhaled corticosteroids is continuously increased, while another drug is also taken for maintenance treatment. If the asthma is still uncontrolled, then oral corticosteroids are added. Because long-term use of corticosteroids is associated with side effects, the guidelines state that inhaled and oral corticosteroids should be used at the lowest doses at which asthma control is maintained, and other treatments should be considered to minimise the use of oral corticosteroids. Eosinophilic asthma is a subtype of asthma, with inflammatory cellular infiltration in the airway. It can be associated with allergy, higher risk of exacerbations, hospitalisation, dependency on oral corticosteroids and increased risk of dying. Biologic treatments for people with severe eosinophilic asthma that is inadequately controlled, despite taking high-dose inhaled corticosteroids and long-acting beta-agonists, aim to both reduce the number and severity of exacerbations and reduce or avoid the use of oral corticosteroids.

Frequency of exacerbations

The number of exacerbations in the previous year influences the treatment pathway

3.4 The committee considered the population of patients proposed by the company (that is, people with a blood eosinophil count of 300 cells per

microlitre or more, who have had 3 or more exacerbations in the previous year or are taking maintenance oral corticosteroids). It considered 2 groups of people according to the treatment options that would be available to them: those who have had 3 exacerbations and are not taking oral corticosteroids, and those who have had 4 or more exacerbations or are taking oral corticosteroids. This overlaps with the populations who are eligible for mepolizumab and reslizumab. Mepolizumab is recommended for adults with a blood eosinophil count of at least 300 cells per microlitre, who have had 4 or more exacerbations needing systemic corticosteroids in the previous year or have taken oral corticosteroids continuously for the previous 6 months. Reslizumab is recommended in adults with a blood eosinophil count of at least 400 cells per microlitre, who have had 3 or more exacerbations needing systemic corticosteroids in the previous year.

Comparators

Mepolizumab is the relevant comparator for people who have had at least 4 exacerbations or are taking maintenance oral corticosteroids

3.5 The committee considered the place of benralizumab in the treatment pathway. It heard from the clinical experts that reslizumab is not frequently used in clinical practice because it is given intravenously, which is not convenient for patients. The committee concluded that mepolizumab is the relevant comparator for people who have had 4 or more exacerbations in the previous year, or who are taking maintenance oral corticosteroids.

Standard care is the relevant comparator for people who have had 3 exacerbations and are not taking oral corticosteroids

3.6 People who have had 3 or more exacerbations in the previous year and have a high eosinophil count (400 cells per microlitre or more) would be eligible for reslizumab. However, the clinical experts noted that the intravenous injections are a disadvantage and limit its use. The committee concluded that for people who have had 3 exacerbations and are not taking oral corticosteroids, the most appropriate comparator in current NHS practice is standard care.

Clinical effectiveness

Benralizumab is more clinically effective than standard care in the clinical trial populations

3.7 The company's clinical evidence comes from 3 trials: SIROCCO, CALIMA and ZONDA. These are randomised-controlled trials comparing benralizumab with placebo in people with uncontrolled asthma, taking inhaled corticosteroids and a long-acting beta-agonist. SIROCCO and CALIMA included people who had 2 or more exacerbations in the previous year and a blood eosinophil count of 300 cells per microlitre or more. ZONDA included people who had 1 or more asthma exacerbations in the previous year and a blood eosinophil count of 150 cells per microlitre or more. The primary outcome in SIROCCO and CALIMA was annual asthma exacerbation rate, and in ZONDA it was the percentage reduction in oral corticosteroid dose from baseline. The committee noted that the pooled results of SIROCCO and CALIMA show that benralizumab reduces the annual rate of exacerbations by 43% compared with placebo (risk ratio [RR] 0.57, 95% confidence interval [CI] 0.47 to 0.69; $p<0.0001$) in the intention-to-treat population. The results also suggest that benralizumab is more clinically effective in people with a blood eosinophil count of 300 cells per microlitre or more, or in people who had 3 or more exacerbations. In a pooled subgroup analysis of people with a blood eosinophil count of at least 300 cells per microlitre who had 3 or more exacerbations, benralizumab significantly reduced the annual asthma exacerbation rate by 53% compared with placebo (RR 0.47, 95% CI 0.32 to 0.67; $p<0.001$). Results from the intention-to-treat analysis from ZONDA showed that benralizumab reduced the median final oral corticosteroid dose by 75% from baseline, compared with a reduction of 25% for placebo (median treatment difference 37.5%, 95% CI 20.8 to 50.0; $p<0.001$). Although the pooled SIROCCO and CALIMA data showed that benralizumab reduced the annual exacerbation rate the committee noted that the absolute reduction depends on the baseline rate, which is related to the severity of the asthma before treatment began. For

example, for the same relative reduction, people who have had 4 or more exacerbations will experience a greater numerical reduction in exacerbations than people who have had 2 or more exacerbations. The clinical experts also explained that treatment will be more effective in people who have a higher blood eosinophil count than those with a lower blood eosinophil count. The committee concluded that benralizumab is clinically effective as an addition to standard care in people with a blood eosinophil count of at least 300 cells per microlitre, who have had 3 or more exacerbations or are taking maintenance oral corticosteroids.

The clinical effectiveness of benralizumab compared with reslizumab and mepolizumab is highly uncertain

3.8 The committee noted that the company did not do a network meta-analysis to compare the clinical effectiveness of benralizumab with reslizumab and mepolizumab, because of significant differences in the trials for these 3 drugs. Instead, it did an anchored matched-adjusted indirect comparison (MAIC) to adjust for differences in patient characteristics between the trials. However, this was only feasible for the comparison with mepolizumab. The company argued that differences in the baseline characteristics of the reslizumab trial prevented a MAIC being done. Instead, the company assumed that benralizumab and reslizumab have the same clinical efficacy. The ERG agreed that a MAIC comparing benralizumab with reslizumab is not feasible, but it noted that there is no evidence to support the assumption of clinical equivalence. The committee agreed that no evidence had been provided to support this assumption and it concluded that the relative efficacy of benralizumab and reslizumab could not be determined. However, the committee noted that reslizumab is used much less frequently than mepolizumab in the NHS, and it considered that the comparison of benralizumab with reslizumab is not critical to its decision making. The committee noted that the MAIC with mepolizumab showed no significant differences between benralizumab and mepolizumab. However, a numerical advantage of one over the other was shown, depending on whether data from the MUSCA trial were

included in the analysis. MUSCA was a 24-week trial that was not included in the MAIC by the company because the primary outcome was health-related quality of life. Without the MUSCA data, the results favoured benralizumab but the reverse was the case if MUSCA data were included. The committee further noted that the MAIC comparing benralizumab with mepolizumab was done in the full trial populations, because relevant subgroup data were not available for mepolizumab. The relative effect was assumed to apply to the subgroup of people with a blood eosinophil count of 300 cells per microlitre or more, who had 4 or more exacerbations. The committee heard from the company that the MAIC matched benralizumab patients to those in the mepolizumab trial, but the relative difference in efficacy between the 2 treatments is assumed to be the same in the most severe subgroup as in the intention-to-treat population. The committee considered that the rationale for the MAIC had not been adequately justified. It also considered that the rationale is inconsistent with the company's use of the clinical-effectiveness estimates from the MAIC, which were applied to a population with different characteristics. The committee noted that a network meta-analysis of mepolizumab and reslizumab could have been done, and this might have been useful for its decision-making. However, it noted that a network meta-analysis may be affected by heterogeneity in the characteristics of the trial populations. The committee therefore concluded that the clinical effectiveness of benralizumab compared with reslizumab and mepolizumab is highly uncertain because the company had made a simple assumption of equivalence for reslizumab, and the method used for the comparison with mepolizumab was not considered robust.

The company's economic model

The model structure is appropriate for decision making

3.9 The company submitted a 4-state Markov model comparing benralizumab with mepolizumab, reslizumab and standard care in people with a blood eosinophil count of at least 300 cells per microlitre, who had had 3 or

more exacerbations or were taking maintenance oral corticosteroids. The committee noted that assessment of response was modelled at 52 weeks, when 'responders' continued taking the biologic and 'non-responders' started standard care. In clinical practice, people have their asthma reassessed every year but this was not included in the company model. The efficacy and clinical parameters in the model were derived from pooled SIROCCO and CALIMA data, ZONDA data, the MAIC results for the comparison of benralizumab with mepolizumab, published literature and previous NICE appraisals. The committee noted that the clinical effectiveness of benralizumab compared with mepolizumab was based on a MAIC, which it had reservations about (see section 3.8). However, the committee considered it commendable that the model attempted to incorporate some of the long-term complications of oral corticosteroid use in the model, even though some effects cannot be reversed so some steroid-sparing benefits may not be realised. Taking everything into account, the committee accepted that the model structure is appropriate for decision making.

Clinical inputs to the model

The model overestimates the proportion of people taking maintenance oral corticosteroids at baseline in the comparison with mepolizumab

3.10 The proportion of people taking maintenance oral corticosteroids at baseline in the company's model was taken from Kerkhof (2017). Different proportions of maintenance oral-corticosteroid use at baseline were used, depending on the comparator (54.1% for standard care and 78.6% for mepolizumab). The ERG preferred a figure of 47.1% for both, sourced from a UK registry of patients with severe asthma (Heaney 2010). The clinical experts stated that in clinical practice in the UK, about 60% of people starting to take mepolizumab will be taking maintenance oral corticosteroids. The proportion of people taking maintenance oral corticosteroid at baseline for the comparison of benralizumab with mepolizumab would therefore be lower than the company's estimate of

78.6%. The committee concluded that the company's model overestimates the proportion of people taking maintenance oral corticosteroids at baseline, for the comparison of benralizumab with mepolizumab. The committee also reiterated that standard care is the only appropriate option for people who have had 3 exacerbations and are not taking maintenance oral corticosteroids.

Asthma-related mortality estimates are overestimated and do not reflect clinical practice in the NHS

3.11 The committee noted that asthma-related mortality is often a key driver of cost effectiveness in asthma models. It noted that the company included both asthma-related mortality and all-cause mortality in its model, and that overall mortality was about 1.5 times higher than all-cause mortality in the UK population. It heard from the clinical experts that the National Review of Asthma Deaths (NRAD) report indicated that asthma-related deaths have decreased substantially in all age categories, except in people over 75. The clinical experts explained that asthma-related deaths are rare, with about 300 to 400 deaths annually in the UK. They commented that some deaths originally recorded as asthma-related in the NRAD report were later found not to have been caused by asthma. They noted that the asthma-related mortality estimate for people 65 years and over in the company's model is implausibly high at 4.54%. The committee concluded that the asthma-related mortality estimates in the company's model are too high, and if lowered this would increase the incremental cost-effectiveness ratio (ICER).

The company's base-case economic analysis

The company's ICER is £34,284 per quality-adjusted life year (QALY) gained compared with standard care

3.12 The company's base-case deterministic ICER is £34,284 per QALY gained for benralizumab compared with standard care in people who had 3 or more exacerbations in the last 12 months, with or without oral corticosteroids, and the probabilistic ICERs give similar results. The

company's estimates of cost effectiveness for benralizumab using the patient access scheme (PAS) price for benralizumab and list prices for mepolizumab and reslizumab found that benralizumab dominated in both comparisons (that is, benralizumab is clinically superior and cost-saving). The ERG provided the committee with an analysis of the cost effectiveness of benralizumab compared with mepolizumab and reslizumab using the PAS prices for the comparators, the results of which are confidential and cannot be reported.

The ERG's exploratory economic analysis

The ERG's preferred exploratory base-case ICER is £39,135 per QALY gained compared with standard care

3.13 The ERG did 5 exploratory analyses considering the whole population of people with 3 or more exacerbations, who are or are not taking oral corticosteroids. It investigated the impact of individual assumptions (that is, asthma-related mortality, maintenance oral corticosteroid use at baseline, alternative administration costs of biologics, weight-based dosing for reslizumab and discontinuation rate) on the ICER for benralizumab compared with standard care, mepolizumab and reslizumab. The key drivers of the cost-effectiveness analysis were asthma-related mortality and maintenance oral-corticosteroid use at baseline in the model. The ERG's preferred assumptions resulted in a deterministic ICER of £39,135 per QALY gained compared with standard care. Further exploratory subgroup analyses resulted in an ICER of £48,883 per QALY gained in the subgroup of people with 3 or more exacerbations who are not taking maintenance oral corticosteroids, and £30,278 per QALY gained in the subgroup of people who are taking maintenance oral corticosteroids.

Cost-effectiveness estimates

For people for whom standard care is the appropriate treatment option (people who have had 3 exacerbations and are not taking oral corticosteroids),

the ICER is above the range normally considered a cost-effective use of NHS resources

3.14 The committee considered the population of people who have had 3 exacerbations and are not taking maintenance oral corticosteroids. This represents a relatively large number of patients. They are not eligible for mepolizumab, and reslizumab is not often used in UK clinical practice, so standard care is the appropriate comparator. The committee was provided with an estimated ICER for benralizumab compared with standard care in a mixed population of 3 or more exacerbations, including people who were and were not taking oral corticosteroids, of between £34,300 per QALY gained (the company's base case) and £39,100 per QALY gained (the ERG's base case). People who have had 3 exacerbations and are not taking oral corticosteroids have less severe disease than some others in the company's total proposed population, and the absolute treatment effect of benralizumab is therefore likely to be lower than the average for the total population in the company's model. The ICER could therefore be considerably higher than estimated by the company and the ERG. The committee concluded that benralizumab could not be recommended for treating severe eosinophilic asthma in people who have had 3 exacerbations and are not taking oral corticosteroids.

For people for whom mepolizumab is the appropriate treatment option (people who have had 4 or more exacerbations or are taking oral corticosteroids), the ICER is above the range normally considered a cost-effective use of NHS resources

3.15 The committee considered the population of people who have had 4 or more exacerbations, or are taking maintenance oral corticosteroids. Taking into consideration the PAS prices for benralizumab and mepolizumab, the committee noted that benralizumab was clearly not cost effective. The committee acknowledged that there is some benefit for benralizumab, particularly in the method and frequency of administration. However it noted that the QALY gain for benralizumab in the company's model is small, and based on an assumption of superior clinical benefit for

benralizumab from the MAIC. The committee did not accept the MAIC as robust (see section 3.8). The committee concluded that benralizumab is not cost effective compared with mepolizumab for treating severe eosinophilic asthma in people who have had 4 or more exacerbations or who are taking oral corticosteroids.

Innovation

3.16 There are no additional benefits that are not captured in the QALY calculations

3.17 The committee noted that benralizumab results in near-complete depletion of blood eosinophils within 24 hours of the first dose, and this depletion is maintained throughout the treatment period. Mepolizumab and reslizumab indirectly reduce the activation, proliferation, and survival of eosinophils resulting in eosinophil reduction but not near-complete depletion. Complete loss of eosinophils could be beneficial, however it could theoretically carry some risks. The clinical experts commented that benralizumab is the only biologic available as a pre-filled syringe, and that is has a more convenient 8-week dosing schedule. People are not currently able to self-administer benralizumab at home, but this might become possible in future. Home administration, together with the reduced dosing schedule, would reduce the administration costs compared with mepolizumab. The clinical experts expressed the opinion that the differences in mode of action for benralizumab compared with mepolizumab and reslizumab are not of themselves innovative, but the convenience of administration of benralizumab would ease some of the burden of living with severe eosinophilic asthma. The committee concluded that benralizumab would be beneficial for patients, but it had not been presented with evidence that there are additional benefits that had not been captured in the cost-effectiveness analyses.

4 Proposed date for review of guidance

4.1 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.

Jane Adam
Chair, appraisal committee
April 2018

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 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.

Sana Khan
Technical Lead

Eleanor Donegan

Technical Adviser

Thomas Feist

Project Manager

ISBN: [to be added at publication]