

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Benralizumab for treating severe eosinophilic asthma

## 1 Recommendations

1.1 Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if:

- the person has agreed to and followed the optimised standard treatment plan and
- they have an eosinophil count of 300 cells per microlitre or more, either are taking maintenance oral corticosteroids or have had 4 or more exacerbations in the past 12 months, or both (that is, are eligible for mepolizumab), or
- they have an eosinophil count of 400 cells per microlitre or more with 3 or more exacerbations in the past 12 months (that is, are eligible for reslizumab).

Benralizumab is recommended only if the company provides it according to the commercial arrangement (see [section 2](#)).

1.2 If benralizumab, mepolizumab or reslizumab are equally suitable, start treatment with the least expensive option (taking into account drug and administration costs).

1.3 At 12 months:

- stop benralizumab if the asthma has not responded adequately, or

- continue benralizumab if the asthma has responded adequately and assess response each year.

An adequate response is defined as:

- a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or
- a clinically significant reduction in continuous oral-corticosteroid use while maintaining or improving asthma control.

1.4 Benralizumab is not recommended if neither mepolizumab nor reslizumab are options (that is, for people with a blood eosinophil count of less than 400 cells per microlitre, who have had 3 or fewer exacerbations in the past 12 months and are not taking continuous oral corticosteroids).

1.5 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. Continuous oral corticosteroids may be needed to prevent exacerbations (asthma attacks) but they can cause long-term side effects. Some people are able to have mepolizumab or reslizumab, which are recommended for slightly different populations. They are biological treatments, as is benralizumab. Biological treatments help to control the asthma, and may 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. In an indirect comparison of benralizumab with mepolizumab, there is no difference in asthma exacerbations.

The company's mixed population is not suitable for considering the cost effectiveness of benralizumab compared with standard care. This is because it is a population of people with a blood eosinophil count of 300 cells per microlitre or more, who have had 3 or more exacerbations in the previous year, and includes some people who are taking maintenance oral corticosteroids. This combines people who are eligible for mepolizumab or reslizumab with other people with less severe disease who are not eligible for biological treatments and can only be offered standard care. The absolute treatment benefit and cost effectiveness of benralizumab varies depending on whether patients are eligible for mepolizumab and reslizumab and what their individual treatment options are.

For people who cannot have mepolizumab or reslizumab and standard care is the only option (that is, with an eosinophil count of less than 400 cells per microlitre, who have had 3 or fewer exacerbations in the last 12 months and are not taking oral corticosteroids), the clinical effectiveness of benralizumab is uncertain. This is because these people comprised a small percentage of the trial population and the cost-effectiveness estimates are higher than can be considered cost effective.

Benralizumab is clinically and cost effective compared with mepolizumab for people with an eosinophil count of 300 cells per microlitre, who have had 4 or more exacerbations or are taking maintenance oral corticosteroids, or both. It is also cost effective compared with reslizumab for people with a blood eosinophil count of 400 cells per microlitre or more, who have had 3 or more exacerbations in the past 12 months.

Therefore it can be recommended for people who could have mepolizumab or reslizumab.

## 2 Information about benralizumab

<b>Marketing authorisation indication</b>	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 $\beta$ -agonists.'
<b>Dosage in the marketing authorisation</b>	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.
<b>Price</b>	The list price is £1,955.0 per 30 mg pre-filled syringe (company submission). The company has a commercial arrangement (patient access scheme). This makes benralizumab 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 ([section 6](#)) 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 an additional treatment option that may reduce 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 inadequately controlled severe eosinophilic asthma is frequently treated with oral corticosteroids. NICE guidance recommends biological treatments such as [mepolizumab](#) and [reslizumab](#) for some people with inadequately controlled eosinophilic asthma. The patient expert explained that these 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, particularly if it reduces or avoids the use of oral corticosteroids.

**Benralizumab could offer an easier method of administration than reslizumab, and a more convenient dosing schedule than existing biological treatments**

3.2 The clinical experts explained that benralizumab is given by subcutaneous injection using a pre-filled syringe (mepolizumab is also given by subcutaneous injection). This is an easier method of administration compared with reslizumab, which is given by intravenous injection. The dosing schedule for benralizumab is more convenient and needs fewer hospital visits than reslizumab and mepolizumab, which are both given every 4 weeks. 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 to be potentially very beneficial for patients.

The patient expert highlighted that benralizumab would be preferred by many patients because its mode of administration and dosing schedule need 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 biological treatments, by reducing visits to hospital, which could be important for people with severe eosinophilic asthma.

### ***Clinical management and comparators***

#### **Benralizumab is a biological agent, and mepolizumab and reslizumab are relevant comparators**

- 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. Biological 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. The committee concluded that benralizumab, although having a slightly different mechanism of action to mepolizumab and reslizumab, also acts by reducing eosinophils, and these are therefore appropriate comparators for benralizumab.

**There is insufficient evidence to recommend benralizumab for people who would not currently be offered biological treatments**

3.4 The clinical experts explained that patients with uncontrolled asthma who have a blood eosinophil count of at least 300 cells per microlitre, and have had at least 3 exacerbations needing systemic corticosteroids in the past 12 months, are referred to specialist asthma centres. These are commissioned by NHS England to be prescribers of the existing biological treatments for eosinophilic asthma (reslizumab and mepolizumab). At the specialist centre the patient's asthma control is optimised on standard treatment, which may bring the symptoms under control. This is done before the need and eligibility for biological treatment is assessed. This in part explains why uptake of mepolizumab and reslizumab is seemingly low, because patients having optimised care at specialist centres may not need a biological treatment. Also patients may choose not to have the existing biologicals because the dosing schedules can be difficult to maintain, the treatment is potentially life-long, and there is limited long-term evidence on their use. The clinical experts explained that the system for commissioning existing biologicals is working efficiently and represents established clinical practice in the NHS (in line with [NICE's methods guide section 6.2.2 and 6.2.3](#)). They did not consider it appropriate at present to use a lower eligibility threshold for treatment with benralizumab than for the existing biologicals. The committee concluded that controlled access to biologicals is working efficiently in the NHS and it is appropriate to consider benralizumab alongside the existing biologicals and that there is insufficient evidence at present for widening access to include people with less severe asthma (that is, people with lower blood eosinophil counts and fewer exacerbations than are specified in the current NICE

recommendations for mepolizumab or reslizumab and are not taking maintenance oral corticosteroids).

### **The choice of comparator depends on oral-corticosteroid use, eosinophil count and the number of exacerbations**

3.5 The committee noted that the clinical trials recruited people with 2 or more exacerbations in the previous year. It noted that the company proposed a sub-population of 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. The company considered that this represents people with more severe eosinophilic asthma, who it considers will get the most benefit from benralizumab. The committee agreed to consider this population but noted that it includes people with differing severity of asthma (defined by eosinophil level, baseline oral-corticosteroid use and the number of exacerbations in the previous year). It therefore includes people who would be offered different treatment options in the NHS:

- people with a blood eosinophil count of 300 cells per microlitre or more, who have had at least 4 exacerbations in the previous 12 months or who are taking oral corticosteroids, can have mepolizumab
- people with a blood eosinophil count of 400 cells per microlitre or more, who have had at least 3 exacerbations in the previous 12 months, can have reslizumab
- people with a blood eosinophil count of 300 to 399 cells per microlitre, who have had exactly 3 exacerbations in the previous 12 months and are not taking oral corticosteroids, would be offered standard care because they are not eligible for a biological treatment.

## ***Clinical effectiveness***

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

3.6 The company's clinical evidence comes from 3 randomised-controlled trials: SIROCCO, CALIMA and ZONDA. These compared benralizumab with placebo in people with uncontrolled asthma, taking high-dose inhaled corticosteroids and a long-acting beta-agonist, who had not already had treatment with any biological. 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 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 exacerbations will experience a greater numerical reduction in exacerbations than people who have had 2 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, but the size of the benefit will be greater for patients who have had more exacerbations with higher eosinophil counts.

**The comparison of the mixed population with standard care is not appropriate for the purposes of decision making**

3.7 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). The committee noted that the clinical trials included people with 2 or more previous exacerbations, and that the company's submission had excluded people with 2 exacerbations and only included people with more severe eosinophilic asthma (3 or more exacerbations) on the basis that people with more severe asthma would benefit most from benralizumab treatment. The committee noted that the absolute effectiveness of benralizumab will be greater in people with more severe disease (that is, those who have had more exacerbations and/or with a higher eosinophil count). It noted that the range of asthma severity in the company's proposed population, which it based on the populations in the clinical trials, may not be generalisable to people who have benralizumab in clinical practice in England. It considered this to be a key area of uncertainty, which will have a large impact on the clinical and cost effectiveness of benralizumab in any 'mixed' population. The committee was particularly interested in the proportion of patients included in the

mixed population who had exactly 3 exacerbations (including those with an eosinophil count between 300 and 399 cells per microlitre and not taking maintenance oral corticosteroids, who are not eligible for treatment with a biological), because this represents a widening of the population that would be eligible for biologicals. It noted that the company provided a range-estimate for the proportion of people in this population in response to the second appraisal consultation document (which is academic in confidence), and noted that this represents a small proportion of the overall mixed population. The company used the lowest proportion in the range to model the cost-effectiveness estimates for benralizumab. The committee concluded that the company's mixed population is based entirely on the patient populations included in the trials, and is not appropriate for decision making. Standard care alone would be a comparator only for people who have had exactly 3 exacerbations, who have an eosinophil count of between 300 to 399 cells per microlitre and are not taking maintenance oral corticosteroids. This represents a very small group of people with less severe disease, who would not currently be eligible for biological treatment. The remaining patients in the mixed population would be eligible for the existing biologicals, but some may choose to have standard care. The committee concluded that the mixed population is not suitable for the purposes of decision making, and that standard care alone is not an appropriate comparator for all patients. It is more appropriate to consider the clinical and cost effectiveness of benralizumab in relation to the eligibility of patients for other treatments available in the NHS (based on the severity of disease defined by oral-corticosteroid use, eosinophil count and the number of exacerbations), rather than considering standard care alone as an appropriate comparator for all patients.

**The clinical-effectiveness estimates for benralizumab are uncertain in the subgroup of people who are not currently eligible for biologicals**

3.8 The committee considered the clinical effectiveness of benralizumab for people who would not currently be eligible for a biological. It noted that the

rate ratio for marginal annual exacerbations from a pooled SIROCCO and CALIMA subgroup analysis was 0.39 for this population. It concluded that this analysis was based on small patient numbers and that it is too soon to consider widening the population eligible for benralizumab, based on a small subgroup analysis and limited efficacy data.

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

3.9 The committee noted that the company did not do a network meta-analysis (NMA) to compare the clinical effectiveness of benralizumab with reslizumab and mepolizumab, because of the significant differences in the patient populations in the trials for these 3 drugs. The company argued that it is more appropriate to adjust for differences in patient characteristics between the trials using an anchored matched-adjusted indirect comparison (MAIC), rather than an NMA. However, this was only feasible for the comparison with mepolizumab because differences in the baseline characteristics of the people in the reslizumab trial prevented a MAIC being done. Instead, the company made the simple assumption 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. The committee noted that the MAIC with mepolizumab showed no significant differences between benralizumab and mepolizumab. However, a non-significant 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 favour benralizumab but the reverse is the case if MUSCA data are included. The committee 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 company explained that the MAIC matched people having benralizumab to people in the mepolizumab trial, and it assumed that the relative difference in efficacy between the 2 treatments is the same in the most severe subgroup as in the intention-to-treat population. The committee considered that despite the rationale provided by the company during consultation, the use of the MAIC instead of an NMA 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 an NMA of mepolizumab and reslizumab could have been done, and this might have been useful for its decision making. However, it noted that an NMA may be affected by heterogeneity in the characteristics of the trial populations. The committee therefore concluded that there remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab and reslizumab because the method used for the comparison with mepolizumab is not considered robust and a simple assumption of equivalence, with no underpinning evidence, was used for reslizumab.

### ***The company's economic model***

#### **The model structure is appropriate for decision making**

3.10 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 biological treatments and 'non-responders' started standard care. The committee noted that the model

included a stopping rule but it was unclear if response was reassessed every year. It considered that treatment continuation based on annual reassessment is appropriate, because people have their asthma reassessed every year in clinical practice and this is consistent with NICE's guidance on [reslizumab](#). 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 considerable reservations about (see section 3.9). 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 proportion of people taking maintenance oral corticosteroids at baseline in the comparison with mepolizumab and standard care is uncertain**

3.11 In response to consultation the company provided an updated model, which included an updated confidential discount to the list price of benralizumab and used many of the model inputs preferred by the committee. Different proportions of maintenance oral-corticosteroid use at baseline were used, depending on the comparator (54.1% for standard care and 60% for mepolizumab). The ERG preferred a value of 41.7% sourced from a UK registry of patients with severe asthma (Heaney 2010) for the standard care comparison, and a value of 60% for the mepolizumab comparison. The clinical experts confirmed that in clinical practice in the UK, about 66% to 80% of people starting to take mepolizumab will be taking maintenance oral corticosteroids. The committee noted that it is difficult to determine the proportion of people

taking maintenance oral corticosteroids in the company's mixed population (see section 3.7). This is a key area of uncertainty in the model, which has a substantial impact on the cost effectiveness of benralizumab.

### **The amended asthma-related mortality estimates are appropriate**

3.12 The committee noted that asthma-related mortality is often a key driver of cost effectiveness in asthma models. 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. The committee noted that in the model provided by the company in response to the first appraisal consultation document, asthma-related mortality was updated to include an average probability of death of 0.0078 per hospital admission (sourced from the British Thoracic Society asthma audit for people aged 45 to 54 years and 55 to 64 years). This was preferred by the committee. The committee concluded that the asthma-related mortality estimates in the company's revised model are appropriate.

### ***The company's updated base-case economic analysis***

#### **The company's mixed population is not suitable for making decisions about the cost effectiveness of benralizumab relative to standard care**

3.13 The committee considered the mixed population proposed by the company of 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 modelled population requires assumptions to be made about the proportion of patients who would be considered for benralizumab in clinical practice depending on use of maintenance oral corticosteroids, number of prior exacerbations, and

blood eosinophil count. The committee noted that within this population some people would be eligible for treatment with other biologicals, and it was therefore only interested in the ICER compared with standard care in people who were not eligible for biologicals (see section 3.16). The committee concluded that the base-case deterministic ICER in the mixed population for benralizumab compared with standard care provided by the company in response to consultation (£25,192 per QALY gained) and the ERG exploratory analysis (£25,587 per QALY gained) are not relevant to decision making. For these reasons, the committee did not consider it appropriate to base its decision making on the ICER from a mixed population that is based solely on proportions from the trials.

### **When mepolizumab is a treatment option, benralizumab is a cost-effective use of NHS resources**

- 3.14 The committee considered people who are eligible for treatment with mepolizumab (that is, people who are taking oral corticosteroids or have had 4 or more exacerbations, with an eosinophil count of 300 cells per microlitre or more). It noted that when the updated PAS price of benralizumab and the PAS price for mepolizumab are used in the model the ICER is below £20,000 per QALY gained. However, the QALY gain for benralizumab compared with mepolizumab in the company's model is small and is based on an assumption of superior clinical benefit for benralizumab from the MAIC, which the committee did not accept as robust (see section 3.9). The committee considered benralizumab to have similar overall health benefits to mepolizumab although it acknowledged that there is some benefit for benralizumab, particularly in the method and frequency of administration. It was reassured that benralizumab and mepolizumab were shown to have similar long-term costs in a cost-comparison done by the ERG, which assumed equal efficacy and used PAS prices and estimated administration costs. The committee therefore concluded that benralizumab is cost effective in people who are eligible for mepolizumab. Given the lack of clear evidence of superiority of one over the other, the committee concluded that if both were equally suitable

for the patient, the least expensive option should be chosen (taking into account drug and administration costs).

**When reslizumab is a treatment option, benralizumab is a cost-effective use of NHS resources**

3.15 The committee considered people who are eligible for treatment with reslizumab (that is, people who have an eosinophil count of 400 cells per microlitre or more and have had at least 3 exacerbations). It noted that when the PAS prices for benralizumab and reslizumab were used in the ERG analysis, benralizumab is clearly cost effective compared with reslizumab. Although the simple assumption of clinical equivalence between the 2 treatments is questionable, it is reasonable to assume that they are not very different. The committee concluded that benralizumab can be considered cost effective for people who are eligible for reslizumab. It acknowledged the potential benefit of benralizumab, particularly in the method and frequency of administration compared with the intravenous administration of reslizumab and concluded that if both were equally suitable for the patient, the least expensive should be chosen (taking into account drug and administration costs).

**When standard care is the only treatment option, benralizumab is not a cost-effective use of NHS resources**

3.16 The committee considered the population for whom standard care is the only treatment option (that is, people with an eosinophil count between 300 to 399 cells per microlitre, who have had exactly 3 exacerbations and are not taking oral corticosteroids). The clinical experts explained that many people with inadequately controlled eosinophilic asthma who are not eligible for treatment with biologicals would have oral corticosteroids, rather than continuing on inhaled medication alone. The committee noted that the company proposed the use of benralizumab earlier in the treatment pathway than existing biologicals are currently used, and it would therefore need to be convinced of the clinical and cost effectiveness of benralizumab in this specific population. It recalled that

the clinical experts consider it is too soon to widen the benralizumab-eligible population to include a new population of patients with less severe disease (see section 3.7) and noted the uncertainty about the clinical effectiveness of benralizumab in these patients (see section 3.8).

Therefore the cost-effectiveness estimates for this population in the company's model are highly uncertain. The committee noted that the company's ICER for benralizumab compared with standard care in people who are not eligible for biologicals (£38,304 per QALY gained) is above the range considered a cost-effective use of NHS resources. It also heard from the ERG that this ICER is associated with significant uncertainty because a very small patient sample was used to obtain the updated transition probabilities and utility values. The committee noted that when the same transition probabilities as those used in the base-case population are used, the ICER increases to £45,406 per QALY gained. It concluded that the most plausible ICER is uncertain for the population that is not eligible for biologicals, but it would be above the level that is considered a cost-effective use of NHS resources.

- 3.17 Having concluded that benralizumab was cost effective in the population for whom mepolizumab or reslizumab were currently recommended, the committee noted that the guidance on these drugs included a recommendation to review the need for continued treatment at 12 months. It further noted that the summary of product characteristics for benralizumab says that a decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. The committee agreed that the recommendation for reviewing treatment every 12 months that applied to the other biologicals was equally appropriate for benralizumab.

## ***Innovation***

- 3.18 The committee acknowledged the advantages to patients of an 8-weekly dosing regimen. It noted that reduced administration costs were included in the economic modelling, which it considered reasonable.

- 3.19 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 biological treatment available as a pre-filled syringe, and that it 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. 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 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.
- 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 severe eosinophilic asthma and the doctor responsible for their care thinks that benralizumab is the right treatment, it should be available for use, in line with NICE’s recommendations.

## **5 Proposed date for review of guidance**

- 5.1 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

December 2018

## **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.

**Sana Khan**

Technical Lead

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Technical Adviser

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Project Manager

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