

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal determination**

**Mepolizumab for treating severe refractory  
eosinophilic asthma**

**1 Recommendations**

1.1 Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and
- the person has agreed to and followed the optimised standard treatment plan and:
  - the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
  - the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and
- the company provides the drug with the discount agreed in the patient access scheme.

1.2 At 12 months of treatment:

- stop mepolizumab if the asthma has not responded adequately or
- continue treatment if the asthma has responded adequately and assess response each year.

An adequate response is defined as:

- at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or
- a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.

1.3 This guidance is not intended to affect the position of patients whose treatment with mepolizumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

<b>Description of the technology</b>	Mepolizumab (Nucala, GlaxoSmithKline) is an anti-interleukin5 humanised monoclonal antibody that reduces circulating eosinophils, which are involved in allergic response and tissue inflammation.
<b>Marketing authorisation</b>	Mepolizumab has a marketing authorisation in the UK as an 'add-on treatment for severe refractory eosinophilic asthma in adult patients'.
<b>Adverse reactions</b>	Headache is a very common adverse reaction. Common adverse reactions are lower respiratory tract infection, urinary tract infection, pharyngitis, hypersensitivity reactions, nasal congestion, upper abdominal pain, eczema, back pain, administration-related reactions, local injection site reaction and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
<b>Recommended dose and schedule</b>	The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. It is intended for long-term treatment, but the summary of product characteristics states that 'the need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations'.
<b>Price</b>	The list price of mepolizumab is £840 per dose (excluding VAT; company submission). The company has agreed a patient access scheme with the Department of Health. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

## 3 Evidence

The appraisal committee ([section 7](#)) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

## 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of mepolizumab, having considered evidence on the nature of severe refractory eosinophilic asthma and the value placed on the benefits of mepolizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

### ***Clinical practice***

- 4.1 The committee understood that severe refractory eosinophilic asthma is a distressing and socially isolating condition. The committee heard from the patient expert that 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 committee heard from clinical experts that standard treatment for severe refractory eosinophilic asthma is oral systemic corticosteroids. It heard that although a patients' disease can respond rapidly to oral systemic corticosteroids, the treatment is associated with long-term complications (such as diabetes mellitus, weight gain, bone loss, immunosuppression, raised blood pressure, and mood swings). The patient expert explained that patients would welcome treatment options that replace the need for corticosteroids. The committee concluded that there was a need for alternative treatments for people with severe refractory eosinophilic asthma.

### **Diagnosis**

- 4.2 The committee discussed the diagnosis of severe refractory eosinophilic asthma in clinical practice. The committee heard from clinical experts that there are no standard diagnostic criteria. Clinicians use the patient's phenotype to come to a probable diagnosis, and confirm this with diagnostic tests for eosinophilia (either peripherally in the blood, from induced sputum, exhaled nitric oxide levels or biopsy specimens from nasal polyps). The committee heard that the peripheral blood eosinophil count was a commonly used biomarker, but when used alone it is not sensitive because eosinophil counts can be suppressed by corticosteroids. The clinical experts stated that measuring sputum eosinophils is more specific, but this is not widely used in clinical practice because it is resource intensive. The committee acknowledged the complexity of diagnosing and monitoring eosinophilic asthma but concluded that blood eosinophil count was a common method for diagnosis.

## **Treatment**

- 4.3 The committee heard from clinical experts that treatment for asthma in clinical practice follows [guidelines](#) from the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). The clinical experts explained that the management of severe eosinophilic asthma lies within what was previously known as step 4 and step 5 of the superseded 2014 version of the British Thoracic Society and SIGN [guidelines](#). The current guidelines (2016) indicate that those people having high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) should be referred for specialist care. The committee heard from clinical experts and during consultation that it was important to encourage patients to adhere to existing optimised standard therapy before trying newer treatments. The committee also understood that oral systemic corticosteroids are used either for short periods to manage an exacerbation, or for longer periods as maintenance treatment when it is difficult to wean people off corticosteroids. The committee concluded that in clinical practice in the NHS, people with severe refractory eosinophilic asthma who have adhered to an optimised standard treatment plan (that is high-dose therapies [previously step 4], or continuous or frequent use of oral corticosteroids [previously step 5]) might be offered mepolizumab by a specialist.

## ***Population***

- 4.4 The committee discussed the population relevant to this appraisal. It was aware that the marketing authorisation for mepolizumab specifies 'refractory' disease. The committee heard from the clinical experts that the term was not used in practice, and they were unable to specifically define 'refractory'. The committee was aware that in the company's submission, populations were further defined by eosinophilia count, frequency of exacerbations, and whether or not patients were treated with continuous oral corticosteroids:

- **Eosinophilia count:** the committee was aware that the company's proposed populations at the first committee meeting included a criterion of blood eosinophil count of 150 cells/microlitre or more when starting treatment. The committee heard from the clinical experts that a threshold of 150 cells/microlitre was considered within the normal range. The clinical experts confirmed that a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months better reflects clinical practice. In its response to the first appraisal consultation document, the company presented evidence using a threshold of 300 cells/microlitre. The committee concluded that a population based on a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months would be relevant to clinical practice.
- **Frequency of exacerbations:** the committee noted that the clinical trials recruited people with 2 or more exacerbations in the previous year. It noted that the company's proposed populations included a criterion based on 4 or more exacerbations per year, to identify the most severe patient group which would gain the most benefit from mepolizumab. The committee acknowledged consultation comments from professional groups that this was appropriate. The committee agreed to consider the population with 4 or more exacerbations.
- **Maintenance oral corticosteroids:** the committee heard from the clinical experts that they would wish to treat people who were having high dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5 of the [British Thoracic Society and SIGN guidelines](#)), with mepolizumab. The committee noted that one of the clinical trials, SIRIUS, showed that mepolizumab reduced maintenance oral corticosteroid use. SIRIUS's criterion for maintenance oral corticosteroids was prednisolone or equivalent 5.0 to 35 mg/day in the 6 months before the start of the study. The committee concluded that the population should be defined as in the SIRIUS trial, that is, having continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg/day in the 6 months before the start of treatment.

In summary, the committee agreed that the most appropriate population, based on the evidence presented by the company, was adults in whom:

- the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and
- the person has agreed to and followed the optimised standard treatment plan and:
  - the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
  - the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months

### ***Clinical effectiveness***

4.5 The committee considered the clinical evidence presented by the company. It noted that the evidence came from 3 randomised double-blind placebo trials:

- MENSA (n=576): the committee noted that the population included people with severe refractory eosinophilic asthma and a history of 2 or more exacerbations needing treatment with systemic corticosteroids in the previous 12 months. Some patients were also on maintenance oral corticosteroids. Patients stayed on their standard maintenance treatment throughout the run-in, trial and follow-up.
- DREAM (n=616): the committee noted that the inclusion criteria were similar to MENSA. Patients stayed on their standard asthma maintenance treatment throughout the trial unless a change was authorised. The primary endpoint was the number of clinically significant exacerbations of asthma during the study, which needed oral or systemic corticosteroids.
- SIRIUS (n=135): the committee noted that the study included a phase at the start in which patients had their corticosteroids optimised; thereafter, only patients on a stable dose of corticosteroids were randomised. The committee noted that the SIRIUS criterion for

maintenance oral corticosteroids was prednisolone or equivalent 5.0 to 35 mg/day in the 6 months prior to the study. The primary endpoint was the number of participants with the indicated percent reduction from baseline in oral corticosteroid dose during weeks 20 to 24 while maintaining asthma control.

The committee agreed that the clinical trials were broadly generalisable to clinical practice.

### **Mepolizumab dose**

- 4.6 The committee noted that mepolizumab has a marketing authorisation at a dose of 100 mg given subcutaneously every 4 weeks. The committee was aware that the company presented clinical-effectiveness evidence for the licensed 100 mg dose, as well as a 75 mg intravenous dose. The committee heard from the company that the regulators considered the 2 doses to be equivalent, which was supported by the clinical experts at the committee meeting. The committee concluded that it would consider the evidence presented by the company both for mepolizumab 75 mg given intravenously and 100 mg given subcutaneously.

### **Mepolizumab compared with placebo**

- 4.7 The committee discussed whether mepolizumab lowered the rate of exacerbations. The company presented pooled results from the 75 mg intravenous and 100 mg subcutaneous groups of MENSA (see table 1). The committee noted that mepolizumab was associated with a lower rate of clinically significant exacerbations in all trials compared with placebo. The committee acknowledged that these results were less clear in SIRIUS, but recognised that the objective of SIRIUS was to reduce oral corticosteroid use; it was not statistically powered to measure exacerbations. The committee heard from clinical experts that mepolizumab is an effective treatment for severe eosinophilic asthma. The committee concluded that mepolizumab reduced the rate of clinically significant exacerbations compared with placebo.



4.8 The committee considered whether mepolizumab reduced the use of oral corticosteroids. The odds ratio of reducing corticosteroids while maintaining asthma control between 20 and 24 weeks was 2.39 (95% confidence interval [CI] 1.25 to 4.56) in SIRIUS compared to placebo. The committee concluded that results showed that mepolizumab reduced the use of oral corticosteroids.

**Table 1 Clinically significant exacerbation rate ratios for mepolizumab compared with placebo**

<b>Analysis (study and dose)</b>	<b>Modified intention-to-treat population (95% confidence interval)</b>
<b>MENSA</b> (75 mg intravenously)	0.53 (0.40 to 0.72)
<b>MENSA</b> (100 mg subcutaneously)	0.47 (0.35 to 0.64)
<b>MENSA pooled</b> (75 mg intravenously and 100 mg subcutaneous)	0.50 (0.39 to 0.65)
<b>DREAM</b> (75 mg intravenously)	0.52 (0.39 to 0.69)
<b>SIRIUS</b> (100 mg subcutaneously)	0.68 (0.47 to 0.99)
<b>DREAM + MENSA</b> (75 mg intravenously or 100 mg subcutaneously)	0.51 (0.42 to 0.62)
<b>DREAM + MENSA + SIRIUS</b> (75 mg intravenously or 100 mg subcutaneously)	Not possible

**Mepolizumab compared with omalizumab**

4.9 The committee noted that the company had identified omalizumab as a comparator in a small ‘overlap’ population who also had severe persistent allergic IgE-mediated asthma and therefore could have either mepolizumab or omalizumab. The committee noted that the company stated that mepolizumab was likely to be a cost-saving option compared with omalizumab in its response to the second appraisal consultation document.

- It heard that clinicians would decide which drug is most appropriate for people based on their phenotype; for example, people with

predominantly eosinophilic symptoms, such as nasal polyps and sinusitis, would be offered mepolizumab, whereas those with predominantly IgE-related symptoms, such as eczema and urticaria, would be offered omalizumab. The committee acknowledged that the 2 drugs were associated with different pathways and different populations. The committee noted comments in response to the first appraisal consultation document that comparing mepolizumab with omalizumab is inappropriate and agreed that there are few people whom clinicians would consider equally likely to have either drug.

- The committee noted that the company had presented a network meta-analysis comparison for mepolizumab and omalizumab and that there were differences between the trial populations in the number of exacerbations in the previous year (mepolizumab trials, 2 or more; omalizumab trials, 1 or more). The committee heard from the company that it did not present an analysis including people from the omalizumab trials with 2 or more exacerbations in the previous year because it did not have access to the data for omalizumab.
- The committee concluded that the results from the company's network meta-analysis comparison of mepolizumab with omalizumab were not robust.

The committee concluded that the comparison was not clinically relevant or methodologically robust and therefore did not consider this comparison further.

### ***Cost effectiveness***

#### **Continuation criteria**

- 4.10 The committee discussed how the company's model incorporated the criteria for continuing treatment with mepolizumab. The committee was aware that the summary of product characteristics for mepolizumab specifies that treatment is reviewed at least once a year, but does not give the criteria for continuing treatment. The committee heard from the clinical experts that treatment would be considered clinically effective if either

people remain stable (that is, they have fewer or the same number of exacerbations than in the previous year) or if the number of exacerbations does not change but the dose of corticosteroids is lowered. The committee recognised that the accepted population specified that a person has had 4 or more asthma exacerbations **or** the person has had continuous oral corticosteroids (see section 4.4), and agreed that the appropriate continuation criteria, to reflect clinical benefit, would be different for each group.

4.11 The committee considered the evidence from the company, presented in response to the second appraisal consultation document, which incorporated continuation criteria based on reducing exacerbations. The committee noted that the continuation criteria were consistent with the evidence on exacerbation rate reduction from the DREAM and MENSA trials (see table 1). It noted that the company provided 2 continuation criteria based on a reducing exacerbations:

- A 50% reduction in exacerbations, suggested by specialists with experience in severe asthma in their response to the first appraisal committee, and proposed in the company response to the second appraisal consultation document and
- A 30% reduction based on an estimate of a clinically meaningful reduction in exacerbations from literature and also proposed by the company in its response to the second appraisal consultation document.

The committee noted that applying different criteria for whether or not to continue treatment affected the incremental cost-effectiveness ratios (ICERs), and therefore considered both approaches in its evaluation of cost effectiveness.

4.12 The committee discussed the company's proposed continuation criteria that treatment with mepolizumab should continue if there is a clinically meaningful reduction in maintenance oral corticosteroid dose.

- The committee heard from the evidence review group (ERG), that the economic model did not fully reflect the benefits of reducing oral maintenance corticosteroids as it was based on data from MENSA, for which the trial protocol stipulated the dose of oral corticosteroid could not be reduced.
- The company acknowledged that because of a lack of evidence, it was not possible to estimate the utility benefit of reducing the dose of oral corticosteroids.
- At the committee's third meeting, the ERG provided analyses with a continuation criterion for reduced oral corticosteroid dose only while maintaining control of asthma during the previous 12 months. The company also stated that the committee could consider estimates based on the original continuation criterion (that is, that treatment can continue if there is no worsening of exacerbations) as an upper bound for the new continuation criteria. However, the committee recalled that both these analyses were based on MENSA, which specified that the oral corticosteroid dose was maintained.

The committee agreed that because of the lack of evidence, it was not possible to accurately model a continuation criterion associated with maintenance oral corticosteroid use. It therefore based its decision making on analyses including a continuation criteria based on exacerbation rates.

#### **Age at start of treatment**

- 4.13 The committee noted that in the base case of the company's original model, the mean age of patients starting treatment was 50.1 years. At the first appraisal committee meeting, the committee heard from the clinical experts that in practice, people are probably younger than this. The committee noted that the company presented a scenario with a starting age of 30 years, which increased the company's base-case ICER. The clinical experts stated that 30 years was younger than the people that they saw in clinical practice in the UK. The committee recognised that the

starting age was an important driver of the model. The committee was aware that the results in NICE's technology appraisal guidance on [omalizumab for asthma](#) were based on a weighted average of the ICERs for different age groups to reflect differing mortality risk by age. The committee agreed that UK registry data or other observational data would help provide the age distribution of people in clinical practice and validate the model.

4.14 A range of evidence was presented to committee regarding the age of the population relevant to the appraisal, which it considered:

- After consultation, the company presented data from the British Thoracic Society, a cross-sectional registry study, and a historical cohort study giving average ages for starting treatment as 50.0, 44.9 and 45.0 respectively. The committee interpreted this to suggest that the age in the UK was likely to be lower than 50 years.
- At the third appraisal meeting, the committee noted that the company kept the starting age in the base case as 50.1 years. In its response to the second appraisal meeting, the company had argued that the proposed population for mepolizumab is recognised to have late-onset eosinophilic disease. The company supported this by citing a registry study by the British Thoracic Society, Newby et al (2014), that included a cohort of 245 people who had late-onset eosinophilic asthma with a mean age at the study start of 49 (standard deviation 14.6) years, and an age at onset of symptoms of 34.5 (standard deviation 16.5) years.
- A more recent publication was also presented by Sweeney (2016) et al reporting on 2 populations with severe asthma, 770 patients from the British Thoracic Society registry (data collected from the UK dedicated Specialist Difficult Asthma Services) and 808 patients in the Optimum Patient Care Research Database (a UK respiratory database containing anonymised primary care data). The British Thoracic Society registry showed a mean age of 50 (standard deviation 14.5) and the Optimum Patient Care Research Database showed a mean age of 59 (standard deviation 17). The company argued that the registry included

all phenotypes of asthma, whereas people with eosinophilic asthma present at older ages than people with other phenotypes. The committee heard from the company that this data, being cross-sectional, did not reflect the age at onset, which would be lower.

The ERG did sensitivity analyses to assess the effect of this uncertainty about the age of onset on the ICER for mepolizumab compared with standard care. The committee noted that the ICER was higher when the age of onset of treatment was lower. The committee concluded that there was some evidence to suggest that the age of onset of treatment was lower than the company's estimate and agreed to take this into account when making its decision.

#### **Age-adjusted mortality rates**

- 4.15 The committee discussed the mortality rates in the company's model. The committee was aware that mortality rates affected the cost effectiveness of mepolizumab. It also noted that the company used Watson et al. (2007) for data on 'mortality after an exacerbation resulting in hospitalisation', and that this resulted in a constant rate of asthma-related mortality for people aged 45 years and over. The committee agreed with the ERG that stratifying mortality into narrower age bands, including having a different rate for 65 years and above, gave a more plausible measure of asthma-related mortality. The committee noted the company used the ERG's preferred approach to estimate the asthma-related mortality in its response to the second appraisal consultation document and concluded that this was appropriate.

#### **Duration of treatment**

- 4.16 The committee discussed the duration of treatment in the company's model. The committee noted that the company assumed that patients with severe refractory eosinophilic asthma would stay on treatment for a maximum of 10 years and that disease response to mepolizumab would not decrease over time. The committee acknowledged comments from the ERG that treating for a lifetime was more appropriate. In its response to

the second appraisal consultation document, the company used a lifetime duration in revised analyses and the committee concluded that this was appropriate.

#### **Duration of benefit of treatment**

- 4.17 The committee discussed the length of benefit from treatment with mepolizumab assumed by the company in its model. The committee noted the ERG's comments that although there is no evidence of a waning treatment effect, the evidence did not show continuous long-term effectiveness either (see [committee papers](#) and section 4.21 of the second appraisal consultation document). In its response to the second appraisal consultation document, the company explained that the benefit (from fewer exacerbations, reduced oral corticosteroid dose and the scores from the asthma control questionnaire) does not decrease over time and that there was no reason to expect a waning treatment effect. It heard from the company that this was supported by longer-term data from the COSMOS trial. Although acknowledging this, the committee noted that there was limited follow-up in the COSMOS follow-on study, and agreed that there was some uncertainty associated with the long-term treatment effect of mepolizumab. However, the committee recognised that with the inclusion of continuation criteria (see section 4.12), if treatment was no longer effective, it would be stopped and concluded that a benefit lasting over the lifetime of the model was acceptable.

#### **Utilities**

- 4.18 The committee discussed the most appropriate measure for utility values. It noted that in its response to the second appraisal consultation document, the company used baseline EQ-5D values from DREAM. In this revised analysis, EQ-5D values were adjusted for a difference in the baseline utility values. This was because the EQ-5D values for the mepolizumab and standard care groups differed at the start of the trial, despite randomisation. The committee heard from the company that this imbalance underestimated the improvement in EQ-5D scores in patients

on mepolizumab compared with standard care. The committee concluded baseline adjustment was appropriate for decision-making.

4.19 The committee discussed other revised assumptions underpinning the utilities used by the company in its response to the second appraisal consultation document:

- **The effect of age on utility:** The committee noted that the company did not adjust utilities by age because DREAM showed there was no difference between age and utility. The committee considered the ERG's comment that DREAM was not powered to detect age-dependent utilities, and noted that there were fewer patients underpinning the data for utilities in older people. The committee was aware of the NICE [technical support document 12](#) that suggests using age-adjusted utility values in decision models. It heard from the ERG that utilities should reflect the effect of age on the general population. The committee concluded that it preferred the ERG's base case, which applied age-adjusted utilities.
- **The effect of the duration of exacerbations on the duration of disutility associated with exacerbations:** In its response to the second appraisal consultation document, the company applied a value that was midway between MENSA and Lloyd et al. for the duration of disutility from exacerbations. The company proposed that the disutility from an exacerbation could last longer than the length of the exacerbation. The committee noted the ERG's comments that taking the average length of exacerbations from MENSA could underestimate the duration of the disutility from exacerbations. The committee also noted the ERG's comments that using the midpoint between MENSA and Lloyd et al. instead of the value from MENSA only had a small effect on the ICER. The committee concluded that the company's alternative approach to estimating the duration of disutility associated with an exacerbation was acceptable.
- **Quality-of-life benefit with mepolizumab, as well as avoiding exacerbations:** The committee discussed whether mepolizumab not



only improved quality of life because of fewer exacerbations, but also because of improved symptom control and lung function. In its response to the second appraisal document, the company presented an analysis from DREAM showing that mepolizumab increased quality of life (using the St George's Respiratory Questionnaire), independent of the effect of reducing exacerbations, compared with placebo. However, the committee noted the ERG's comment that these differences could have been confounded by fewer exacerbations, and was aware that the ERG did not have access to the individual patient data to validate the company's analyses. The committee noted comments in response to consultation, suggesting that mepolizumab offers benefits beyond a reduction in exacerbations. The committee concluded that mepolizumab was likely to improve symptoms as well as reducing exacerbation rates.

#### **Cost-effectiveness results**

4.20 The committee considered the company's cost-effectiveness results in the 'accepted population'. The committee recalled its preferred assumptions, and concluded that the ERG's base case, which the ERG entitled its 'most plausible', most closely matched the committee's preferred assumptions on:

- rates for asthma-related mortality (see section 4.15)
- percentage of patients meeting continuation criteria (based on COSMOS; see section 4.12)
- mean age of 'accepted population' (51.5 years; see section 4.13)
- duration of disutility associated with exacerbations (midpoint between MENSA and Lloyd et al.; see section 4.19)
- treatment dependent EQ-5D (baseline adjusted for difference in treatment arm; see section 4.18).

4.21 The committee noted the results of the ERG's ICERs for mepolizumab compared with standard care:

- £31,895 per quality-adjusted life year (QALY) gained, using the original continuation criterion (that is, that treatment can continue if there is no worsening of the annual number of exacerbations).
- £31,378 per QALY gained, using a continuation criterion of a 30% reduction in exacerbations in the first year.
- £29,163 per QALY gained, using a continuation criterion of a 50% reduction in exacerbations in the first year.

The committee noted that when a continuation rule that specifies a 50% reduction in exacerbations in the first year was applied, the ICER was £29,163 per QALY gained. The committee recognised, however, that if patients in the NHS were younger than the starting age modelled at the beginning of treatment (45 years), the ICER would increase to £32,557 per QALY gained. The committee also acknowledged that there were adverse effects associated with the use of long-term systemic corticosteroids that were not captured in the modelling and accounting for these would reduce the ICER. The committee concluded that mepolizumab, as an add-on to optimised standard therapy, could be recommended as an option for treating severe refractory eosinophilic asthma in adults for the 'accepted population' when a continuation criteria of 50% reduction in exacerbation was applied.

- 4.22 The committee noted that the population included people receiving maintenance oral maintenance corticosteroids, and that a continuation criterion relating to a reduction in exacerbations could not apply to this group. The committee recognised the challenges in modelling the benefits of reducing maintenance oral corticosteroid, and therefore also a related continuation rule. It recognised the company had proposed the continuation criterion '*clinically meaningful reduction in maintenance oral corticosteroid dose*'. The committee took a pragmatic view and agreed this would be appropriate provided asthma control was also maintained or improved, as this reflected a treatment benefit. The committee concluded that the appropriate continuation rule was: a clinically significant reduction

in continuous oral corticosteroid use while maintaining or improving asthma control.

### ***Innovation***

4.23 The committee heard from stakeholders that mepolizumab is innovative in its potential to have a significant and substantial effect on health-related benefits. The committee heard from clinical experts that mepolizumab is a novel treatment, with which the committee agreed. The committee discussed the analysis presented by the company to capture the benefits of reducing oral corticosteroid use, separate to any benefits from reducing exacerbations. It heard from the ERG and the company that, because of the designs of the trials that the company had used, there were limitations in the analyses (section 4.12). The committee agreed that benefits related to minimising the significant adverse effects of systemic corticosteroid use had not been fully captured in the QALY measure. The committee also considered that there were benefits to carers, which may not have been captured in estimating the QALY gain associated with mepolizumab. The committee therefore agreed that mepolizumab could be considered innovative.

### ***Pharmaceutical Price Regulation Scheme (PPRS) 2014***

4.24 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the

PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.

**Summary of appraisal committee’s key conclusions**

TAXXX	Appraisal title: mepolizumab for treating severe refractory eosinophilic asthma	Section
<b>Key conclusion</b>		
<p>Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:</p> <ul style="list-style-type: none"> <li>• the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and</li> <li>• the person has agreed to and followed the optimised standard treatment plan and: <ul style="list-style-type: none"> <li>– the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or</li> <li>– the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and</li> </ul> </li> <li>• the company provides the drug with the discount agreed in the patient access scheme.</li> </ul>		1.1
<p>At 12 months of treatment:</p> <ul style="list-style-type: none"> <li>• stop mepolizumab if the asthma has not responded adequately or</li> <li>• continue treatment if the asthma has responded adequately and assess response each year.</li> </ul>		1.2

<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	Severe refractory eosinophilic asthma is a distressing and socially isolating condition. Exacerbations can be life threatening and can happen without warning. The committee heard that standard treatment is oral systemic corticosteroids. Patients would welcome treatment options that replace the need for corticosteroids.	4.1
<b>The technology</b>		
Proposed benefits of the technology  How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from clinical experts that mepolizumab is a novel treatment that reduces exacerbations and offers the potential to reduce corticosteroid use.	4.23

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee understood from clinical experts that the management of severe eosinophilic asthma lies within what was previously known as step 4 and step 5 of the superseded 2014 version of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) guidelines. The current guidelines (2016) indicate that those people having high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) should be referred for specialist care.</p>	<p>4.3</p>
<p>Adverse reactions</p>	<p>The summary of product characteristics lists headache as a very common adverse reaction for mepolizumab. Common adverse reactions also include lower respiratory tract infection, urinary tract infection, pharyngitis, hypersensitivity reactions, nasal congestion, upper abdominal pain, eczema, back pain, administration-related reactions, local injection site reaction and pyrexia.</p>	<p>2</p>
<p><b>Evidence for clinical effectiveness</b></p>		

<p>Availability, nature and quality of evidence</p>	<p>Evidence for mepolizumab compared with placebo came from 3 randomised controlled trials.</p> <p>Evidence for mepolizumab compared with omalizumab came from a network meta-analysis. The trials included different patient populations, including differences in disease severity. The committee concluded that the comparison was not clinically relevant or methodologically robust and therefore did not consider this comparison further.</p>	<p>4.5</p> <p>4.9</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee agreed that the most appropriate population, termed the ‘accepted population’, for this appraisal should be based on the evidence presented by the company, that is, people:</p> <ul style="list-style-type: none"> <li>• the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and</li> <li>• the person has agreed to and followed the optimised standard treatment plan and:             <ul style="list-style-type: none"> <li>– the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or</li> <li>– the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.</li> </ul> </li> </ul>	<p>4.4</p>

<p>Uncertainties generated by the evidence</p>	<p>The committee concluded that the comparison of mepolizumab with omalizumab was not clinically relevant or methodologically robust and therefore did not consider this comparison further.</p> <p>The committee noted that the ICER was higher when the age of onset of treatment was lower. The committee concluded that there was some evidence to suggest that the age of onset of treatment was lower than the company's estimate and agreed to take this into account when making its decision.</p>	<p>4.9</p> <p>4.14</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The committee agreed the most appropriate population, termed the 'accepted population', for this appraisal should be broadly based on the evidence presented by the company, that is, people:</p> <ul style="list-style-type: none"> <li>• the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and</li> <li>• the person has agreed to and followed the optimised standard treatment plan and: <ul style="list-style-type: none"> <li>– the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or</li> <li>– the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months</li> </ul> </li> </ul>	<p>4.4</p>



Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that results showed that mepolizumab reduced the use of oral corticosteroids.	4.8
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The company submitted a de novo Markov model to assess the cost effectiveness of mepolizumab compared with standard care or with omalizumab.	ACD2 3.21
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the ICER was higher when the age of onset of treatment was lower. The committee concluded that there was some evidence to suggest that the age of onset of treatment was lower than the company's estimate and agreed to take this into account when making its decision.	4.14
Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee agreed that benefits related to minimising the significant adverse effects of systemic corticosteroid use had not been fully captured in the QALY measure. The committee also considered that there were benefits to carers, which may not have been captured in estimating the QALY gain associated with mepolizumab.	4.23

<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee agreed the most appropriate population, termed the ‘accepted population’, for this appraisal should be broadly based on the evidence presented by the company, that is, people:</p> <ul style="list-style-type: none"> <li>• the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and</li> <li>• the person has agreed to and followed the optimised standard treatment plan and: <ul style="list-style-type: none"> <li>– the person has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or</li> <li>– the person has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.</li> </ul> </li> </ul>	<p>4.4</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>Exacerbation rates, age-related mortality estimates and attrition rates.</p>	<p>4.21</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee noted that when a continuation rule that specifies a 50% reduction in exacerbations in the first year was applied, the ICER was £29,163 per QALY gained.</p>	<p>4.21</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The company has agreed a patient access scheme with the Department of Health.</p>	<p>1.1</p>

## 5 Implementation

- 5.1 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.
- 5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe refractory eosinophilic asthma and the doctor responsible for their care thinks that mepolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and GSK UK LTD have agreed that mepolizumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

## 6 Review of guidance

- 6.1 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.

Amanda Adler  
Chair, appraisal committee  
November 2016

## **7 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 B](#)

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.

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.

### ***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.

### **Wendy Gidman**

Technical Lead

**Jasdeep Hayre**

Technical Adviser

**Jeremy Powell**

Project Manager

ISBN: [to be added at publication]