

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Mepolizumab for treating severe refractory
eosinophilic asthma**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using mepolizumab 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 base (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 (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using mepolizumab 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: 29 June 2016

Third appraisal committee meeting: 4 August 2016

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

- 1.1 Mepolizumab is not recommended within its marketing authorisation as an add-on for treating severe refractory eosinophilic asthma.
- 1.2 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

- 2.1 Mepolizumab (Nucala, GlaxoSmithKline) is an anti-interleukin-5 humanised monoclonal antibody. By reducing the effects of interleukin-5 mepolizumab reduces circulating eosinophils, which are involved in allergic response and tissue inflammation. Mepolizumab has a marketing authorisation as an add-on treatment for severe refractory eosinophilic asthma in adults, at a dose of 100 mg given subcutaneously every 4 weeks.
- 2.2 The summary of product characteristics lists headache as a very common adverse reaction for mepolizumab. Common adverse reactions also listed 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.
- 2.3 The list price of mepolizumab is £840 per dose (excluding VAT), cited in the company submission. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of mepolizumab, 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 does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by GlaxoSmithKline and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Treatment pathway

3.1 Current British guidelines on [managing asthma](#) from the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment in adults. Control is achieved and maintained by stepping up treatment as needed and stepping down treatment when control is good. The guideline steps are:

- Step 1: Inhaled short-acting beta-2 agonist as needed.
- Step 2: Add inhaled corticosteroid (200–800 micrograms per day).
- Step 3: Add an inhaled long-acting beta-2 agonist. If control is still inadequate, increase the dose of the inhaled corticosteroid to 800 micrograms per day. If there is no response to the inhaled long-acting beta-2 agonist, stop this drug and increase the inhaled corticosteroid dose to 800 micrograms per day. If control is still inadequate, try a leukotriene receptor antagonist or slow-release theophylline.
- Step 4: Consider increasing the dose of inhaled corticosteroid up to 2,000 micrograms per day. Consider adding a fourth drug (for example, a leukotriene receptor antagonist, slow-release theophylline or a beta-2 agonist tablet).
- Step 5: Use daily corticosteroid tablets at the lowest dose providing adequate control. Maintain high-dose inhaled corticosteroid at

2,000 micrograms per day. Consider other treatments to minimise the use of corticosteroid tablets. Refer patients to specialist care.

Clinical effectiveness

- 3.2 The company did a systematic literature review and identified 3 key randomised controlled trials: DREAM, MENSA and SIRIUS. The company also gave supportive evidence from early studies (SB-240563/006, CRT110184 and SB-240563/046) and observational studies that followed on from the trials (COLUMBA and COSMOS). COLUMBA is an ongoing open-label extension to DREAM and will last 3.5 years. COSMOS was an open-label extension to MENSA and SIRIUS and lasted 1 year.
- 3.3 MENSA (n=576) was a multicentre (including UK), phase III, randomised, double-blind trial that compared mepolizumab (75 mg intravenously or 100 mg subcutaneously once every 4 weeks) with placebo for 32 weeks. The population included people aged 12 years and older, with severe refractory eosinophilic asthma on high-dose inhaled corticosteroids, and a history of 2 or more exacerbations in the previous 12 months needing treatment with systemic corticosteroids. Some patients were on maintenance oral corticosteroids. All participants had a blood eosinophil level of either 300 cells/microlitre or more in the 12 months before screening or 150 cells/microlitre or more at screening.
- 3.4 DREAM (n=616) was a multicentre (including UK) phase IIb, randomised, double-blind trial comparing mepolizumab (75 mg, 250 mg and 750 mg, all intravenous, once every 4 weeks) with placebo for 52 weeks. The inclusion criteria were similar to MENSA, including people aged 12 years and older, with severe refractory eosinophilic asthma on high-dose inhaled corticosteroids, and a history of 2 or more exacerbations in the previous 12 months needing treatment with systemic corticosteroids. Some patients were also on maintenance oral corticosteroids. But, eosinophilic airway inflammation was defined as any of the following:

elevated blood eosinophils of 300 cells/microlitre or more; elevated sputum eosinophils of 3% or more; elevated fractional exhaled nitric oxide (FeNO) of 50 parts per billion (ppb) or more; or deteriorating asthma control after reducing the maintenance dose of either inhaled corticosteroids or oral corticosteroids by 25% or less in the previous 12 months.

- 3.5 SIRIUS (n=135) was a multicentre (including UK), phase III, randomised, double-blind trial that compared mepolizumab 100 mg subcutaneously once every 4 weeks, with placebo for 24 weeks. The population included people aged 12 years and older, with severe eosinophilic asthma, who needed regular treatment with maintenance systemic (oral or parenteral) corticosteroids and high-dose inhaled corticosteroids. Like MENSA, all patients in the trial had either a blood eosinophil level of 300 cells/microlitre or more in the 12 months before screening or 150 cells/microlitre or more at screening. 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.
- 3.6 The primary outcome in MENSA and DREAM was the frequency of clinically significant exacerbations of asthma, defined by worsening of asthma that needed systemic corticosteroids or hospitalisation or emergency department visits. The trials did not require that patients be treated with systemic corticosteroids at the start. The primary outcome in SIRIUS was the reduction in oral corticosteroids during weeks 20–24 compared with baseline.
- 3.7 The company presented a modified intention-to-treat (ITT) analysis that included all trial patients who were randomised and had at least 1 dose of study medication. The company presented results to show that participants with more severe disease benefited more from treatment with mepolizumab than patients with less severe disease. To identify a subgroup with the greatest treatment response, the company considered:

sex; age; weight; region; baseline percentage predicted forced expiratory volume in 1 second (FEV₁); airway reversibility; number of exacerbations in the previous 12 months; baseline blood eosinophil count; baseline use of maintenance oral corticosteroids; and blood IgE level. The company used data from DREAM and MENSA in the post hoc analyses. The company stated that baseline blood eosinophil count most strongly predicted treatment response and that patients with a higher historic exacerbation rate (4 or more in the previous 12 months) had a greater numerical reduction in exacerbations per year than those with fewer than 4 exacerbations at baseline.

3.8 Based on these results, and before the committee's first meeting, the company proposed a preferred population for its base-case analysis (hereafter referred to as the 'proposed population'):

- adults with a blood eosinophil count of 150 cells/microlitre or more at the start of treatment (regardless of their value in the year before screening), and
- 4 or more exacerbations in the previous year **or** dependency on systemic corticosteroids.

The company stated its belief that although all patients in the trials are likely to benefit from mepolizumab irrespective of eosinophil levels, the benefits would be greater in the company's chosen population and will ensure an efficient use of NHS resources.

3.9 Before the committee's first meeting, the company also specified a subgroup of the proposed population (the 'restricted population') that excluded patients with fewer than 4 exacerbations in the previous year. This subpopulation included:

- adults with a blood eosinophil count of 150 cells/microlitre or more at the start of treatment, and
- 4 or more exacerbations in the previous year.

Also, in response to a request by the ERG, the company presented results for a group of people in the proposed population who were excluded from the restricted population, that is:

- adults with a blood eosinophil count of 150 cells/microlitre or more at the start of treatment, and
- fewer than 4 exacerbations in the previous year, and
- dependency on systemic corticosteroids.

3.10 All 3 trials reported data on clinically significant exacerbations (with or without hospitalisation). The results for intravenous mepolizumab 75 mg compared with placebo from MENSA and DREAM, and for subcutaneous 100 mg mepolizumab compared with placebo from SIRIUS and MENSA are reported in table 1 and table 2. The recommended dose of mepolizumab is 100 mg given subcutaneously once every 4 weeks. The European Medicines Agency deemed that this was bioequivalent to 75 mg given intravenously once every 4 weeks. But, the incidence of injection-site reactions was higher for mepolizumab given subcutaneously (8%) than intravenously (1.7%). The company presented pooled results from the 75 mg intravenous and 100 mg subcutaneous arms of MENSA and used these pooled results in its meta-analyses and in the model.

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

	Modified ITT population (95% CI)	Proposed population (95% CI)	Restricted population (95% CI)
MENSA (75 mg IV)	0.53 (0.39 to 0.71)	0.40 (0.24 to 0.67)	0.39 (0.22 to 0.68)
MENSA (100 mg SC)	0.47 (0.35 to 0.63)	0.50 (0.32 to 0.78)	0.39 (0.23 to 0.67)
MENSA pooled (75 mg IV and 100 mg SC)	0.50 (0.39 to 0.64)	Not reported	Not reported
DREAM (75 mg IV)	0.52 (0.39 to 0.69)	0.36 (0.24 to 0.55)	0.31 (0.18 to 0.53)
SIRIUS	0.68	0.77	0.81

(100 mg SC)	(0.47 to 0.99)	(0.51 to 1.17)	(0.40 to 1.64)
DREAM + MENSA (75 mg IV or 100 mg SC)	0.51 (0.42 to 0.62)	0.41 (0.31 to 0.55)	0.35 (0.25 to 0.50)
DREAM + MENSA + SIRIUS (75 mg IV or 100 mg SC)	Not possible	0.50 (0.40 to 0.64)	0.42 (0.30 to 0.57)
Abbreviations: CI, confidence interval; ITT, intention to treat; IV, intravenous; SC; subcutaneous.			

Table 2 Rate ratio for exacerbations needing hospitalisation, for mepolizumab compared with placebo

	Modified ITT population (95% CI)	Proposed population (95% CI)	Proposed restricted population (95 % CI)
MENSA (75 mg IV)	0.61 (0.23 to 1.66)	0.28 (0.05 to 1.45)	0.19 (0.03 to 1.31)
MENSA (100 mg SC)	0.31 (0.11 to 0.91)	0.55 (0.15 to 2.03)	0.49 (0.11 to 2.11)
MENSA (75 mg IV or 100 mg SC)	0.44 (0.19 to 1.02)	Not reported	Not reported
DREAM (75 mg IV)	0.61 (0.28 to 1.33)	0.45 (0.14 to 1.43)	0.50 (0.13 to 1.97)
DREAM + MENSA (75 mg IV or 100 mg SC)	0.50 (0.28 to 0.89)	0.44 (0.19 to 1.02)	0.43 (0.16 to 1.12)
Abbreviations: CI, confidence interval; ITT, intention to treat; IV, intravenous; SC; subcutaneous.			

3.11 The primary outcome in SIRIUS was the percentage of patients who reduced their dose of corticosteroids during weeks 20–24, compared with their dose at baseline, while maintaining asthma control. People having mepolizumab were more likely to reduce their dose of corticosteroids compared with placebo with an odds ratio (OR) of 2.39 (95% confidence interval [CI] 1.25 to 4.56) in the modified ITT population, 1.81 (95% CI 0.86 to 3.79) in the proposed population, and 2.75 (95% CI 0.72 to 10.59) in the restricted population.

- 3.12 The company acknowledged that the analyses presented for the subpopulations may not be powered to find any effect of mepolizumab on the occurrence of rarer events; for example, exacerbations needing hospitalisation. But it stated that the trend for both subpopulations was in line with the results from the modified ITT population.
- 3.13 Health-related quality of life was assessed in DREAM using the EQ-5D utility index. EQ-5D data were collected at screening and at 4-weekly intervals until week 52. The median change from baseline EQ-5D score at week 52 was 0.04 for placebo and 0.03 for mepolizumab 75 mg intravenously in the modified ITT population. The company highlighted that at baseline, about one third of patients in DREAM reported an EQ-5D utility score of 1.0 (that is, perfect health), which it considered did not reflect the impact of severe asthma on quality of life and also meant that for this group of patients, any quality-of-life improvement with mepolizumab treatment could not be captured. The company suggested that many patients reported perfect quality of life because EQ-5D does not include a recall period, so it would not capture resolved exacerbations. The company also noted that for patients having 4 or more exacerbations in the previous 12 months, the difference in EQ-5D scores between mepolizumab and placebo was smaller than in the overall modified ITT population. The company stated this suggested that EQ-5D is not an appropriate measure in severe asthma.
- 3.14 Instead, the company presented results based on the St George's Respiratory Questionnaire (SGRQ). This is a disease-specific questionnaire designed to measure health impairment in patients with asthma. In the MENSA and SIRIUS trials, the SGRQ showed that mepolizumab improved quality of life compared with placebo. The company stated that the minimal clinically important difference for SGRQ is 4 units and the differences in MENSA and SIRIUS ranged from 5 to 13 units for all 3 populations. The company noted that SGRQ would

not capture reductions in quality of life during an exacerbation or fear of an exacerbation.

- 3.15 The MENSA and SIRIUS trials also used the Asthma Control Questionnaire to measure the mean change in the score from baseline to the end of the study period. The company stated that the minimum clinically important difference for the Asthma Control Questionnaire is 0.5 and that the results for the modified ITT population indicated that the company's proposed population had greater benefit from mepolizumab treatment compared with placebo.
- 3.16 To estimate the effectiveness of mepolizumab compared with omalizumab, the company carried out a network meta-analysis. The meta-analysis had 3 outcomes: clinically significant exacerbations; exacerbations needing hospitalisation; and change from baseline in predicted FEV₁. The company created separate networks for each outcome.
- 3.17 For mepolizumab, the company used data from MENSA and DREAM. The company noted that omalizumab was only a comparator for mepolizumab for patients who show both allergic (IgE) and eosinophilic phenotypes of severe asthma. The company explored 3 approaches to identifying this population but, due to a lack of data, presented the modified ITT population for mepolizumab. So, the data were based on a population that was eligible for mepolizumab (in line with its marketing authorisation), but only some could have omalizumab (based on the NICE technology appraisal guidance on [omalizumab for treating severe persistent allergic asthma](#), which stipulates that people should have had continuous or frequent oral corticosteroid treatment, defined as 4 or more courses in the previous year).
- 3.18 For omalizumab, the company used data from the omalizumab trials INNOVATE and EXTRA. INNOVATE (n=419) and EXTRA (n=850) were phase 3 randomised, placebo-controlled, double-blind trials comparing

omalizumab with placebo. INNOVATE included people with inadequately controlled severe persistent allergic asthma and EXTRA included people with inadequately controlled moderate to severe asthma. The company included 2 additional open-label randomised controlled trials of omalizumab, Niven (2008) and EXALT, in secondary analyses. The omalizumab trials included patients with 1 or more exacerbations needing treatment with systemic corticosteroids in the previous year. But NICE guidance on [omalizumab for treating severe persistent allergic asthma](#) stipulates that people should have had continuous or frequent oral corticosteroid treatment, defined as 4 or more courses in the previous year. So, the trial data for omalizumab was from a less severe population than would be treated in clinical practice. It also included some patients who would not be eligible for mepolizumab.

- 3.19 The company indirectly compared mepolizumab and omalizumab using a Bayesian random-effects model and a fixed-effect model. For the outcome of clinically significant exacerbations, the rate ratio was 0.664 for mepolizumab compared with omalizumab, indicating fewer exacerbations with mepolizumab. The company acknowledged that the results should be treated with caution because only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and the study populations differed in severity.
- 3.20 The company presented data on adverse events from DREAM, MENSA and SIRIUS. Based on a pooled analysis, the following adverse events were more frequent for mepolizumab than for placebo: eczema (relative risk [RR] 5.34; 95% CI 1.25 to 22.78); nasal congestion (RR 2.62; 95% CI 0.89 to 7.72); and dyspnoea (RR 2.20; 95% CI 0.78 to 6.20). The cumulative incidence of drug-related adverse events was 16% in the placebo group compared with 23% in the group having mepolizumab 100 mg subcutaneously and 18% in the group having mepolizumab 75 mg intravenously. The most frequently reported drug-related adverse events in the placebo group and the groups having mepolizumab 100 mg

subcutaneously and 75 mg intravenously were headache (2%, 5%, and 3% respectively) and injection-site reaction (3%, 6%, and 2% respectively).

Cost effectiveness

3.21 Before the committee's first meeting, the company submitted a de novo Markov model to assess the cost effectiveness of mepolizumab compared with standard care or omalizumab. To compare mepolizumab with standard care, the company presented the results for 3 different populations (defined in sections 3.7–3.9):

- the modified ITT population
- the proposed population
- the restricted population.

To compare mepolizumab with omalizumab, the company presented results based on the modified ITT overlap population who also had severe persistent allergic IgE-mediated asthma, rather than in its proposed population, because it did not have access to patient-level data for omalizumab (see section 3.17).

3.22 The mean age for patients in the model was 50.1 years. The model used a lifetime horizon, with a cycle length of 4 weeks. The company discounted costs and benefits at 3.5% per year and did not apply a half-cycle correction. The company stated that costs were from the perspective of the NHS and social services. The model had 4 health states:

- on treatment pre-continuation assessment
- on treatment post-continuation assessment
- off treatment
- death.

3.23 The model includes a point after 1 year when clinicians assess whether it is appropriate for patients to remain on treatment. People treated with mepolizumab or omalizumab entered the model in the health state 'on treatment pre-continuation assessment' and stayed there until clinicians assessed whether they should continue taking treatment. This happened at different times: at 12 months for mepolizumab and at 16 weeks for omalizumab. Patients moved to the 'on treatment post-continuation assessment' state if they met the criteria to continue treatment. The criterion to continue treatment with mepolizumab was that there must be no increase in the number of exacerbations from baseline. If this was not met, patients entered the 'off treatment' state in which they had standard care and they stayed there until death. Otherwise, patients moved to the 'on treatment post-continuation assessment' state and stayed there until they stopped treatment or died. In its base case, the company assumed that 10% of patients stop treatment every year and that no patients are treated for longer than 10 years. The company also assumed that there was a constant treatment benefit for mepolizumab over time. During each cycle, patients in any health state (except death) could have one of 3 types of clinically significant exacerbations:

- exacerbations needing systemic corticosteroids (or double the maintenance dose)
- exacerbations needing hospitalisation
- exacerbations needing emergency department visits.

The company's model took into account the effect of exacerbations on utility, risk of death, drug acquisition costs, administration costs, monitoring costs and costs associated with managing exacerbations.

3.24 The company based the effectiveness of mepolizumab compared with standard care on the clinically significant exacerbation rates from the MENSA trial and did not pool results across trials or use results from the

network meta-analysis. The data sources for different phases in the model are described in table 3.

Table 3 Data sources utilised for different phases in the model

Model pathway	Data source
First 12 months	Data at 32 weeks from people randomised to mepolizumab in MENSA were used to estimate the mean treatment effect of mepolizumab.
After 12 months – for patients who met the criteria to continue treatment	Patient level data from MENSA at 32 weeks were analysed to determine those patients meeting the 12-month exacerbation continuation criteria and their corresponding exacerbation rate was applied.
After 12 months – for patients who did not meet the criteria to continue treatment	Exacerbation rates from the placebo group of MENSA were used to estimate the exacerbation rates for the standard-care group.

- 3.25 To compare mepolizumab with omalizumab, the company based the effectiveness estimates for clinically significant exacerbation rates on the fixed-effect network meta-analysis during the pre-continuation assessment phase of the model (at 52 weeks for mepolizumab and at 16 weeks for omalizumab). After assessment, clinically significant exacerbation rates from ‘responders’ on the MENSA trial for mepolizumab, and ‘responders’ on the INNOVATE trial for omalizumab were used.
- 3.26 To model mortality, the company assumed that a patient could only die from asthma after a clinically significant exacerbation, which may or may not involve hospitalisation. In the base-case analysis, the company determined mortality rates after exacerbations involving hospitalisation from a study in patients hospitalised for acute severe asthma by Watson et al. (2007). It supplemented this with relative rates of asthma-related mortality outside of hospital, reported in the National Review of Asthma Deaths. The company assumed in its model that patients may die of other causes and used age-dependent transition probabilities for both general mortality and asthma-related mortality.

3.27 The company got utility values for mepolizumab by mapping SGRQ scores in the MENSA trial to EQ-5D (table 4). The mapping algorithm was based on a population with chronic obstructive pulmonary disease (not eosinophilic asthma). The company explored EQ-5D values directly from the DREAM trial in a scenario analysis (table 4). The company assumed that the utility estimates for omalizumab were the same as those for mepolizumab. The company looked to Lloyd et al. (2007) for disutilities associated with exacerbations, which were 0.10 for exacerbations needing oral corticosteroids and 0.20 for exacerbations needing hospitalisation. The company assumed that an exacerbation leading to an emergency department visit would have the same disutility as an exacerbation needing oral corticosteroids (0.10). The company did not include adverse reactions in the model.

Table 4 Utilities in the company’s model

	Modified ITT population		Proposed population		Restricted population	
	EQ-5D	SGRQ mapped	EQ-5D	SGRQ mapped	EQ-5D	SGRQ mapped
Pre-continuation assessment	0.802	0.796	0.827	0.777	0.829	0.793
Standard care (off treatment)	0.794	0.738	0.785	0.708	0.797	0.682
Post-continuation assessment (on treatment)	0.824	0.806	0.837	0.795	0.834	0.805

Abbreviation: SGRQ, St George's Respiratory Questionnaire; ITT, intention-to-treat.

3.28 The company included the following costs in its model: drug acquisition costs; administration costs; monitoring costs; and costs associated with managing exacerbations. The cost of mepolizumab per 4-weekly cycle was assumed to be equal to the price of a 100-mg mepolizumab vial,

which is given once every 4 weeks. The company included the discounted price based on the confidential patient access scheme for mepolizumab in the model. The company based the components of standard care on MENSA and included these in the model at list price. The company included the list price for omalizumab because it did not have access to the discounted price in the confidential patient access scheme. The ERG presented analyses comparing mepolizumab and omalizumab based on their discounted prices. The exact dose of omalizumab depends on body weight and blood IgE level and the company calculated this using 2 different approaches; one incorporating data measuring the dosing distribution of omalizumab in England (resulting in costs of £872.22 per 4-week cycle per person) and the other based on the NICE's technology appraisal guidance on [omalizumab for asthma](#) (resulting in costs of £617.99 per 4-week cycle per person).

3.29 In the company's base case for the modified ITT population, presented to the committee for its first meeting, the probabilistic incremental cost-effectiveness ratio (ICER) was £31,659 per quality-adjusted life year (QALY) gained for mepolizumab compared with standard care. For the company's proposed population, the probabilistic ICER was £19,526 per QALY gained for mepolizumab compared with standard care. For the restricted population the probabilistic ICER was £15,478 per QALY gained for mepolizumab compared with standard care.

3.30 In response to the request from the ERG (see section 3.9), the company presented results for people who:

- had a blood eosinophil count of 150 cells/microlitre or more when starting treatment, and
- were dependent on systemic corticosteroids, and
- had fewer than 4 exacerbations per year.

The deterministic ICER for this group was £78,716 per QALY gained for mepolizumab compared with standard care. The increase in the ICER compared with the other subgroups was because of a lower exacerbation rate, fewer exacerbations needing hospitalisation (and so lower asthma-related mortality), and a smaller difference in the utilities between mepolizumab and the comparator in this subgroup.

- 3.31 The company did a series of univariate sensitivity analyses and scenario analyses. The key driver of the cost effectiveness for mepolizumab compared with standard care was the utility estimate applied to the standard-care arm.
- 3.32 The company also carried out a scenario analysis taking into account the costs and consequences of long-term systemic corticosteroid use. For this, the company estimated the dose-dependent risk of developing 5 adverse events associated with systemic corticosteroid therapy: myocardial infarction; diabetes mellitus; cataracts; osteoporosis; and peptic ulcer. The company assumed that 24% of people in both treatment groups take maintenance oral corticosteroids at baseline, based on the MENSA trial. The company assumed that a proportion of patients stop maintenance treatment with oral corticosteroids and estimated the rate of 'oral corticosteroid sparing' from the median dose reduction in oral corticosteroids with mepolizumab, from SIRIUS at 24 weeks (a median of 30%). The company presented a scenario reflecting stopping, rather than simply reducing, oral corticosteroids and assumed that 6.9% of people treated with mepolizumab – compared with standard care – stopped maintenance oral corticosteroid treatment at 24 weeks (based on SIRIUS). Results based on both approaches had little effect on the ICERs.

ERG comments

- 3.33 The ERG stated that the company's post-hoc modelling analysis to identify the proposed population should be interpreted with caution. The

ERG noted that its clinical advisors agreed that a threshold of 4 or more previous exacerbations was appropriate. But, they questioned a blood eosinophil threshold of 150 cells/microlitre or more, because it is a relatively low count within the normal range, and because eosinophil levels can fluctuate. Instead, the ERG's advisors suggested a blood eosinophil threshold of 300 cells/microlitre in the previous 12 months. The ERG noted that the European Medicines Agency stated that eosinophil levels were not sufficiently predictive to justify a specific cut-off within the marketing authorisation for mepolizumab. So, the ERG questioned whether the findings for the 150 cells/microlitre or more threshold may be because of chance or confounding.

3.34 The ERG was satisfied that the company included all relevant studies in its submission. The ERG noted that the trial durations were relatively short at 24–52 weeks. The ERG also noted that the primary outcome in DREAM and MENSA (clinically significant exacerbations) was a composite outcome, which included:

- using systemic corticosteroids (or double the maintenance dose) or
- hospitalisation or
- hospital emergency department visits.

3.35 The ERG stated that the methods of indirect comparison were appropriate. The ERG noted that there were differences between the trials, including the proportion of people with severe asthma (which was greater in the mepolizumab trials). The ERG considered that this may bias the estimate in favour of mepolizumab because a more severe asthma population could be expected to have a higher treatment effect. The ERG also considered that, given the concerns over differences between studies, the random-effects model was more appropriate than the fixed-effect model for all scenarios and endpoints.

- 3.36 The ERG noted that mepolizumab seems to be generally well tolerated in people with severe eosinophilic asthma. But, there was little long-term safety data available for mepolizumab. The ERG noted that 5–6% of patients on 100 mg mepolizumab developed antibodies to mepolizumab, but the company stated that this did not affect the pharmacokinetics and pharmacodynamics of mepolizumab in most patients.
- 3.37 The ERG stated that its clinical advisers considered a lifetime duration of mepolizumab more plausible than 10 years of treatment, because there is no fixed stopping rule. So, the ERG considered the 10-year stopping rule in the model inappropriate, and carried out exploratory analyses.
- 3.38 The ERG had concerns around the criteria to continue treatment in the model. The ERG stated that the company proposed continuing treatment unless a patient's rate of exacerbation increases. This would mean that a subgroup of patients stay on treatment even when not improving, which may not be aligned with clinical practice. The ERG asked that the company present exploratory analyses linking the continuation criteria with improvement in exacerbations. However, the company stated that quantifying improvement in terms of fewer exacerbations would underestimate treatment benefit because some patients on maintenance oral corticosteroids may not have fewer exacerbations but may instead take lower doses of corticosteroids.
- 3.39 The ERG noted that in the company's model, patients who do not continue mepolizumab have the same rates of exacerbation as patients in the standard-care group. The ERG stated that asthma in those who do not meet the continuation criteria may be more difficult to treat and have higher exacerbations. So, the ERG proposed that having the same exacerbation rate for people on standard care and those who do not meet the continuation criteria may underestimate the exacerbation rate in patients not meeting the continuation criteria.

- 3.40 The ERG stated that the rate of exacerbation chosen by the company for patients who continue mepolizumab could be inappropriate. The ERG noted that these rates were measured in the MENSA trial shortly after patients started treatment, and so might not reflect the long-term effectiveness of mepolizumab. In contrast, the COSMOS study measured rates of exacerbation for a full year in patients who had already been on mepolizumab for 32 weeks. A full year would also account for the seasonal nature of asthma exacerbations. The ERG requested that the company present exploratory analyses using data from COSMOS. But, the company stated that the exacerbation rate in COSMOS in patients treated with mepolizumab during MENSA (0.9%) was similar to that measured in the ITT population in MENSA (0.877%). The ERG noted that these exacerbation rates differ from the rate of 0.55 in the modified ITT population, used in the model for patients on mepolizumab who meet the continuation criteria. The ERG also considered that the SIRIUS study better estimated the rate of exacerbations in people treated with oral corticosteroids than the MENSA trial, because the population in the SIRIUS trial had severe eosinophilic asthma needing maintenance systemic corticosteroids and high-dose inhaled corticosteroids. The ERG carried out exploratory analyses including the exacerbation rates from COSMOS and SIRIUS.
- 3.41 The ERG stated that it would have been more appropriate for the company to model the directly-obtained EQ-5D utility estimates from the DREAM trial, in line with the NICE reference case. The ERG questioned using a mapping algorithm determined in chronic obstructive pulmonary disease rather than asthma.
- 3.42 The ERG noted that the length of utility decrement from exacerbations was based on the study by Lloyd et al. (2007), which assumed a 4-week utility decrement. The ERG noted that the Lloyd et al. study did not report the disutility estimated for exacerbations that needed a visit to an emergency department. The ERG also noted that using the average

duration of the exacerbations in MENSA, instead of the duration of exacerbations based on the Lloyd et al. study, would have been more appropriate.

- 3.43 The ERG considered that the company should have used the mortality rate for asthma from the Roberts et al. (2013) study rather than the Watson (2007) study. The ERG explained that the Watson et al. study measured asthma-related mortality at ages 18–44 years and 45 years and over; so, the study assumed a constant rate of asthma-related mortality for people aged 45 years and over. The ERG considered that the Roberts et al. study gave more accurate asthma mortality estimates because it stratified patients into narrower age bands, including for people aged 65 years and over. The ERG noted that in Roberts et al, the asthma-related mortality rate in people 65 years and over was about 6 times higher than that in the 45–54-years group. The ERG considered that the Watson et al. study overestimated mortality between the ages of 45 years and 65 years and underestimated mortality in people 65 years and over. The ERG concluded that because the median age of the patients in the model was 50.1 years, and because the model treatment duration was 10 years, the model likely overestimated the asthma-related mortality during the treatment period, thereby also overestimating the benefits of mepolizumab.
- 3.44 The ERG considered that the results of the company’s oral corticosteroid sparing analyses should be treated with caution. The ERG noted that the company used data from MENSA to calculate exacerbation rates in mepolizumab patients, yet used data on corticosteroid reduction from a different trial, SIRIUS. The ERG stated that this overestimated the benefits of mepolizumab, because exacerbation rates might not decrease as much when reducing corticosteroid use. The ERG noted the company used a 10-year time horizon instead of a lifetime horizon, as the company did in its base case. The ERG noted that this would underestimate the

benefits of oral corticosteroid sparing because of the chronicity of the adverse effects associated with corticosteroids.

- 3.45 The ERG noted that the company used data related to oral corticosteroid sparing from the modified ITT population of SIRIUS instead of the company's proposed population. The ERG also noted that the company did not consider utility decrement from osteoporotic fractures and considered some utility decrements from chronic conditions only as 'one-off' disutilities. The ERG noted that data relating to the proportion of patients who stop oral corticosteroids differ between this appraisal and in NICE's technology appraisal guidance on [omalizumab for asthma](#): 14.5% of patients stopped oral corticosteroids treatment in SIRIUS compared with 41.9% of those whose disease responded to omalizumab in the technology appraisal. In general, the ERG agreed with the company that the current analyses did not capture the impact on the ICER of reducing oral corticosteroids use.
- 3.46 The ERG carried out a series of exploratory analyses using the company's economic model. The ERG had concerns about the company's proposed population being defined according to blood eosinophil count, noting that if the company had instead chosen to define the population by a blood eosinophil count of 300 cells/microlitre or more in the 12 months before the study, the results would have been very different. The ERG stated that defining a population that has 4 or more exacerbations, and is not restricted by blood eosinophil count, would have been more appropriate. The ERG was unable to do this analysis because it did not have the data.
- 3.47 The ERG explored several scenarios using the company's model (table 5), all of which increased the company's base-case ICER for mepolizumab compared with standard care in all populations.

Table 5 Results of the ERG’s scenario analyses for mepolizumab compared with standard care (includes the patient access scheme for mepolizumab)

	Modified ITT population	Proposed population	Restricted population
Company base case	£31,692	£19,511	£15,478
EQ-5D utilities (DREAM)	£40,932	£20,863	£18,429
Asthma mortality (Roberts et al. 2013; Watson et al. 2007)	£42,728	£27,544	£20,735
Lifetime on biologics	£32,130	£19,763	£15,571
Exacerbation utility decrement from MENSA	£32,480	£19,963	£15,690
Exacerbation rates for patients meeting continuation criteria from COSMOS	£37,190	£22,239	£17,240
ERG base case (combining all 5 amendments above)	£72,596	£35,440	£33,520
Abbreviation: ITT, intention to treat.			

Additional evidence

3.48 After consultation on the appraisal consultation document, the company presented 3 new analyses:

- Analysis 1: patients on maintenance oral corticosteroids who had 2 or more exacerbations in the previous year.
- Analysis 2: patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year.
- Analysis 3: patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year.

3.49 The company did not vary its base-case assumptions, instead exploring some, but not all, of the committee’s preferred assumptions in sensitivity analyses. The company did not explore adjusting utilities or mortality for age. The company’s revised base case analyses resulted in ICERs of £31,734, £22,305 and £22,134 for mepolizumab compared with standard care for analysis 1, 2 and 3 respectively.

- 3.50 The ERG adjusted the company's analyses to include the committee's preferred assumptions (see sections 4.18–4.24). These included:
- age-adjusting mortality data
 - age-adjusting utilities
 - not including a utility gain for treatment with mepolizumab over and above the gain from a reduction in exacerbations
 - using MENSA for the source of the mean duration of exacerbations
 - lifetime treatment duration
 - for those not meeting continuation criteria, exacerbation rates not equal to standard care
 - for those meeting continuation criteria, exacerbation rates based on a similar patient population in COSMOS.

3.51 This resulted in ICERs of £107,499, £57,708 and £59,859 per QALY gained for analysis 1, 2 and 3 respectively. The ERG further explored the impact of using direct EQ-5D values from trials and this reduced the ICERs to £64,216, £48,358 and £50,960 per QALY gained respectively. The ERG also presented scenario analyses exploring a waning effect of mepolizumab and varying the starting age in the model which increased the ICERs.

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 effectiveness

- 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 be life threatening and can happen without warning, causing fear and resulting in frequent 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. The committee heard that patient's disease characteristically responds rapidly to oral systemic corticosteroids, but the drugs are associated with long-term complications. The patient expert explained that these complications include diabetes, weight gain, hip replacement, raised blood pressure, epilepsy and mood swings, all of which can significantly affect patients, and that patients would welcome treatment options that replace the need for corticosteroids. The committee heard that mepolizumab reduces both exacerbations and oral corticosteroid use. The committee concluded that severe refractory eosinophilic asthma is associated with substantial morbidity and that there was a need for alternative treatments.
- 4.2 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) that recommend a step-wise approach to treating adults (see section 3.1). The clinical experts explained that severe eosinophilic asthma is considered to lie within step 4 and step 5 of these guidelines. The committee understood that steps 4 and 5 could be defined as a full trial of, and, if tolerated, documented adherence with inhaled high-dose corticosteroids, long-acting beta-2 agonists, leukotriene receptor antagonists, theophyllines, oral systemic corticosteroids, and smoking cessation. The committee understood that in step 5, oral systemic corticosteroids are used for short periods, for example to manage an exacerbation, or can be used for

longer periods as maintenance treatment. The committee was aware that the marketing authorisation for mepolizumab specifies 'refractory' disease and questioned whether only people under step 5 of the guidelines who have tried all treatment options would be eligible for mepolizumab. The clinical experts stated that the term 'refractory' was not used in practice and could offer no specific definition of 'refractory'. The committee understood that in UK clinical practice, people with uncontrolled severe refractory eosinophilic asthma having treatment described in steps 4 and 5 of the guidelines might be offered treatment with mepolizumab.

4.3 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. It heard that 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). To diagnose eosinophilic asthma, clinicians also observe whether patients respond rapidly to oral corticosteroids. The committee heard that peripheral blood eosinophil count was a commonly used biomarker, but when used alone is not sensitive because counts can be suppressed by using 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.

4.4 The committee discussed the appropriate population for the appraisal. It recognised that before the first committee meeting the company presented 3 different populations defined by eosinophilia count; frequency of exacerbations; and whether or not patients were treated with maintenance oral corticosteroids. The committee first discussed the eosinophilia criterion. The committee was aware that the company's proposed populations included a criterion of blood eosinophil count only of

150 cells/microlitre or more when starting treatment (see table 3). The committee considered the following:

- Advice from clinical experts that a threshold of 150 cells/microlitre or more does not have a clinical basis and would be considered within the normal range. The clinical specialists confirmed that if this test were used, a threshold of 300 cells/microlitre or more better reflects clinical practice.
- Explanation from clinical experts that eosinophil levels fluctuate and systemic corticosteroid treatment suppresses blood eosinophil levels, meaning this measure is not sensitive.
- The European Medicines Agency statement that blood eosinophil levels were not sufficiently predictive to include a cut-off within the marketing authorisation.
- That the company stated it did not intend a blood eosinophil count of 150 cells/microlitre or more to be a diagnostic measure when starting treatment, but rather it chose this group because the results looked more effective, and to improve cost effectiveness.

The committee noted that any subgroup analysis should be based on clinical plausibility and agreed that a population based on a threshold of at least 150 cells/microlitre when starting treatment was not relevant to clinical practice. After consultation, the committee heard that a threshold of 300 cells/microlitre was more appropriate. The committee concluded that a population based on a blood eosinophil count of 300 cells/microliter or more in the previous year would be relevant to clinical practice in the UK.

- 4.5 During its first meeting, the committee considered the value reflecting the frequency of exacerbations used by the company to define the proposed and restricted populations. The committee noted that MENSA and DREAM recruited people with 2 or more exacerbations in the previous year, but the company's proposed populations included a criterion to

include people with 4 or more exacerbations per year. The committee heard from the clinical experts that clinicians would want to offer mepolizumab to people who have 2 or more exacerbations per year, especially for people having maintenance systemic corticosteroids. However, after consultation stakeholders proposed 3 or 4 exacerbations despite full adherence to inhaled systemic corticosteroids as reasonable. The committee concluded that a criterion based on 4 exacerbations was appropriate.

- 4.6 At its first meeting, the committee discussed whether the appropriate population for treatment with mepolizumab would include people who do not take maintenance oral corticosteroids. The experts highlighted that they would wish to see people on step 4 or 5 of the [British Thoracic Society and SIGN guidelines](#), who may not be on maintenance oral systemic corticosteroids, but were having several exacerbations, considered eligible for treatment with mepolizumab. But, the committee was aware that it must make recommendations within the marketing authorisation, which states mepolizumab ‘is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients’. The company, however, confirmed after consultation that ‘refractory’ disease includes people who take maintenance oral corticosteroids as well as people who need several courses of oral corticosteroids during the year. Stakeholders emphasised that mepolizumab is a treatment option for people who may not be on maintenance oral corticosteroids, but who need frequent treatment with oral corticosteroids. The committee heard that reducing the use of oral corticosteroids would be of great value to these people. The committee concluded that the population should not be limited to people dependent on maintenance oral corticosteroids, and discussed how to define the appropriate population in light of this.

- 4.7 The committee noted various suggestions put forward by consultees to define the population. These included using a threshold of 3 or more exacerbations per year along with a threshold of 300 cells/microlitre or

more in the previous 5 years, or including different criteria altogether for people on maintenance oral corticosteroids and those who experience recurrent exacerbations. However, the committee was aware that the company's evidence base did not include results based on these proposed definitions. The committee noted that the company presented new analyses for 3 further populations after consultation (see section 3.48), with analysis 3 put forward as the company's preferred population. The committee noted that this included patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year. Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:

- 4 or more exacerbations in the previous year
- on maintenance oral corticosteroids

would best reflect the population seen in UK clinical practice.

4.8 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, but also a 75-mg intravenous dose and included results from a pooled analysis in the economic model. The committee heard from the company that the 2 doses are bioequivalent, which was supported by the clinical experts. The committee concluded that it would consider the evidence presented by the company for mepolizumab 75 mg intravenously and 100 mg subcutaneously.

4.9 The committee considered the results from the key trials: MENSA, DREAM and SIRIUS. The committee noted that the company presented results based on the modified intention to treat (ITT) population, that is,

people in the ITT population who had had at least 1 dose of treatment. The committee considered that basing analyses on the whole randomised population is more conventional, but heard from the ERG that the modified ITT population excluded very few people and so the committee agreed to discuss these results. The committee noted that mepolizumab, compared with placebo, was associated with a lower rate of clinically significant exacerbations in all trials, but these results were less pronounced in the SIRIUS trial (see table 1). The committee questioned this and heard that the SIRIUS trial was different because its primary objective was to reduce oral corticosteroid use, which would affect exacerbation rates. It also included people having maintenance oral corticosteroids and was not statistically powered to measure exacerbations. The committee heard from clinical experts that mepolizumab is a very effective and novel drug, and an important new development for the treatment of eosinophilic asthma. The committee concluded that, compared with placebo, mepolizumab is effective in reducing the rate of clinically significant exacerbations.

- 4.10 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 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. It noted that the company had presented an indirect treatment comparison using the DREAM and MENSA trials for mepolizumab and the INNOVATE and EXTRA trials for omalizumab. The committee noted that the company based its comparison on the full trial populations, yet 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 company clarified that it did not present an analysis including people from the omalizumab trials with 2 or more exacerbations in the previous year because it only had access to study level published results for omalizumab. The company stated that 1 trial for omalizumab included people with 2 or more exacerbations in the previous year and a better matched analysis may have been possible, although this analysis would be based on data from only 1 trial, rather than 2. The committee acknowledged that the 2 drugs were associated with different pathways and different populations. It also considered that adjusting for these differences in the very small overlap population was unlikely to be robust. The committee noted that the ERG stated that, because of the differences between the trials, the random-effects model was more appropriate than the fixed-effect model preferred by the company. The committee agreed with the ERG but also noted that estimating heterogeneity was difficult because only 2 trials were included in each arm of the network meta-analysis, and therefore uncertainties would remain. The committee concluded that the results from the company's indirect comparison of mepolizumab with omalizumab were highly uncertain and not suitable for decision-making. The committee noted comments from consultation 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 therefore did not consider this comparison further.

- 4.11 During its first meeting, the committee noted that the company had presented no data for using mepolizumab after omalizumab. After consultation, the company clarified that a small number of patients in the MENSA trial were previously treated with mepolizumab (with an interval of 130 days) and that the efficacy was comparable to omalizumab-naive patients in the subcutaneous 100-mg group. The company also presented further data from the MENSA trial stratified by prior omalizumab use,

which showed that there is no evidence of differential effectiveness in people previously treated with omalizumab. The committee concluded that mepolizumab is effective in people previously treated with omalizumab.

Cost effectiveness

4.12 The committee noted that, to compare mepolizumab with standard care, the company presented cost-effectiveness results based on 3 populations before the committee's first meeting:

- the modified ITT population
- the proposed population
- the restricted population (see section 3.21).

After consultation the company presented 3 additional analyses:

- Analysis 1: patients on maintenance oral corticosteroids who had 2 or more exacerbations in the previous year.
- Analysis 2: patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year.
- Analysis 3: patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year.

4.13 The committee recalled its previous conclusion that analysis 3 reflected the most appropriate population available for decision-making (see section 4.7). The committee noted that the company presented cost-effectiveness analyses comparing mepolizumab with omalizumab. The committee was aware that the results from company's indirect comparison underpinned these, and recalled its previous conclusion that the results of the indirect comparison were highly uncertain and not suitable for decision-making. The committee concluded that it would consider the company's analysis for mepolizumab compared with standard care using

the company's analysis 3 population with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:

- 4 or more exacerbations in the previous year
- on maintenance oral corticosteroids.

4.14 The committee discussed the choice of standard care as a comparator in the company's model. In its first meeting, the committee queried whether standard care including maintenance oral corticosteroids was a more appropriate comparator than standard care including oral corticosteroids in short courses. The committee heard from clinical experts that one of the aims of mepolizumab treatment is to reduce use of maintenance corticosteroids and therefore it alone was not an appropriate comparator. In line with this, and its decision on the appropriate population (analysis 3, after consultation) the committee was satisfied that standard care including oral corticosteroids in short courses and with or without maintenance corticosteroids was an appropriate comparator.

4.15 The committee discussed the structure of the company's model and specifically the criteria for continuing treatment with mepolizumab. The committee was aware that the marketing authorisation for mepolizumab specifies that people are reviewed at least once a year, but does not specify the criteria. The committee noted that modelled patients were assessed at 12 months and, as long as their exacerbation rates were not worse than in the previous year, they continued to have mepolizumab. Thereafter, the company assumed that 10% of patients stop treatment each year. The committee heard from the clinical experts that treatment would be considered to be clinically effective if people remain stable (that is, they have fewer or the same number of exacerbations than in the previous year) because the number of exacerbations may not change in people whose dose of corticosteroids was lowered. The committee acknowledged the importance of reducing oral corticosteroid use, but considered that it was generally more appropriate to include continuation

criteria linked with improvement. The committee heard during consultation that the stopping rule should be 'more robust' and heard from the company that its stopping rule allows for clinical flexibility so that people benefiting from a reduction in oral corticosteroid use could continue treatment. The company presented data to show that all people who continued treatment in MENSA had a reduced rate of exacerbations. The ERG, however, stated that this could be because of different lengths of the result collection period rather than a true effect for all patients meeting the continuation criteria. Also, the committee considered that a 10% attrition rate seemed to be arbitrary and did not constitute a formal continuation rule. The committee was aware that assuming higher attrition rates (when also accounting for age-related mortality) would increase the incremental cost-effectiveness ratio (ICER). The committee concluded that continuation criteria linked to improvement would have been more appropriate.

4.16 The committee noted that the company used different sources of evidence for the different exacerbation rates used in the model. The committee discussed the key assumptions for exacerbation rates in the following groups of patients:

- people whose disease did not respond to treatment and they stopped mepolizumab at 1 year
- people whose disease had responded to treatment at 1 year, but beyond 1 year they stopped mepolizumab, and
- people whose disease had responded to treatment at 1 year and they remained on mepolizumab.

4.17 The committee discussed the exacerbation rates for patients who did not meet the continuation criteria and stopped mepolizumab at the end of the first year. The committee heard from the ERG that the company used data from patients who had never been treated with mepolizumab to represent the rate of exacerbations in those who were treated with mepolizumab but

did not meet the criteria to continue. The committee heard from the clinical experts that the company's assumption was not generalisable. To support its assumption, the company provided evidence from a 12-month follow-up study, which showed that after stopping mepolizumab, blood eosinophil levels and asthma exacerbation rates both returned to pre-trial levels. The ERG, however, stated that patients who do not respond to mepolizumab are likely to have more severe disease than patients who do respond and – more importantly – more severe disease than the average patient randomised to standard care, who has never had mepolizumab. Noting that the company had data reflecting the exacerbation rates in people who did not respond to mepolizumab in MENSA, who were then followed-up in COSMOS, the ERG preferred to use these data because they directly reflect patient experience. The ERG noted that the COSMOS extension study measured exacerbation rates for a full year in people who had already been on mepolizumab for 32 weeks. The committee agreed with the ERG that, using the company's assumption, the model would underestimate the exacerbation rates for patients who do not respond to mepolizumab. The committee concluded that it preferred the approach using COSMOS data.

- 4.18 The committee discussed the exacerbation rates for patients who responded to mepolizumab and continued it after the first year, but then stopped later. The committee was aware of the company's assumption that after stopping mepolizumab at any point over the course of the model, patients have the same exacerbation rates as those in the standard-care group. The committee considered that people whose disease had responded were likely to have less severe disease than those whose disease had not responded and so this was an unrealistic assumption. The committee was aware that, for this group, the ERG calculated rates of exacerbation such that the rate for people who had had mepolizumab was lower than for people on standard care. The committee

concluded that the ERG's analysis was more plausible than the company's approach.

- 4.19 The committee discussed the exacerbation rates for patients who responded to mepolizumab during the first year and continued taking it long term. The committee was aware that the company used data for exacerbation rates from MENSA. The committee noted the ERG's comment that exacerbation rates in MENSA were measured shortly after patients started treatment and may not reflect the long-term effect of mepolizumab. The committee heard that this was particularly important because of seasonal fluctuations in exacerbation rates (MENSA was shorter than 1 year). The ERG suggested that data from the COSMOS extension study were more appropriate for those patients who met the continuation criteria, because the study measured exacerbation rates for a full year in people who had already been on mepolizumab for 32 weeks. After consultation, the company presented data for exacerbation rates in COSMOS for patients who met the continuation criteria in MENSA. The company separated out the underlying rate of exacerbations with standard care by either using pre-trial enrolment exacerbation rates, or by using the non-responder exacerbation rates in COSMOS; both approaches resulted in similar results. The ERG stated that the company's approach of using pre-trial rates for standard care (but not for mepolizumab) meant that any placebo effect would be included for mepolizumab but not for standard care; the approach of using 'non-responder' exacerbation rates from COSMOS for patients who responded to mepolizumab was not appropriate because 'non-responders' would be associated with more severe disease. The ERG also stated that for the first year, the rates from MENSA should also have been applied to the standard-care arm. After continuation assessment, the rate for patients continuing on mepolizumab should have been taken from COSMOS. For standard care, the best estimate would be based on MENSA data. The ERG noted that exacerbations in COSMOS were higher than in MENSA for patients on

mepolizumab. Therefore, in its base case, the ERG incorporated the impact of inflating the exacerbation rate in the standard-care group by using the ratio of exacerbations in MENSA and COSMOS for mepolizumab. The committee concluded that the ERG's approach took into account more of the available data on exacerbations and was therefore more appropriate.

4.20 The committee discussed the duration of treatment in its 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. The committee heard from the clinical experts that they would treat people for as long as they benefited. The clinical experts stated that if the disease responded to mepolizumab, they would expect it to continue to do so. But they acknowledged that the long-term effects were currently unknown. The committee noted that the ERG had explored the impact of including a lifetime duration of mepolizumab and concluded that this was appropriate. It noted that this marginally increased the ICER, which it understood was because both costs and benefits increased over a lifetime duration of treatment with mepolizumab.

4.21 The committee discussed the continued lifetime benefit of treatment with mepolizumab assumed by the company in its model. The committee considered that this assumption was optimistic and considered that a scenario exploring a waning effect of mepolizumab would be valuable, which the ERG provided after consultation. The committee noted that reducing the duration of response decreased the cost effectiveness of mepolizumab relative to standard care. The committee heard from the company that there was no clinical reason to expect waning of treatment effect and that this was supported by longer-term data from the COSMOS trial. The committee concluded that the COSMOS follow-on study had

limited follow-up, and that there was a large degree of uncertainty around the long-term results associated with mepolizumab. The committee concluded that it would be mindful that accounting for waning would increase the ICER.

4.22 The committee discussed the estimates of utility in the model. It noted that the company had estimated utility values by mapping St George's Respiratory Questionnaire (SGRQ) scores in the MENSA trial to EQ-5D. The committee noted that directly obtained EQ-5D utility estimates were available from the DREAM trial. The committee noted that the company had justified using SGRQ because it was disease-specific and included a recall period to capture the effect of exacerbations. But the ERG explained that if the mapping exercise were conducted appropriately, any limitations of the EQ-5D would still apply. The company also explained that DREAM was a smaller trial and included an unlicensed dose of mepolizumab (100 mg subcutaneously). However, having accepted that the 2 doses could be considered equivalent the committee did not consider this to be a problem. The committee concluded that direct EQ-5D values were preferable.

4.23 The committee further considered the utilities in the model, noting that:

- The utilities had not been adjusted for age; it heard from the ERG that this would slightly increase the ICER. The company stated that because the starting age in both treatment arms was the same, the effect of this would cancel out, but the ERG explained that this assumption would not hold because mepolizumab is associated with fewer deaths. The committee agreed that utilities should be age adjusted.
- The company modelled separate disutilities associated with exacerbations, which the committee considered could 'double count' disutility. The committee concluded that this may have overestimated the utility values for mepolizumab.

- The company assumed that each exacerbation lasted 28 days, which came from Lloyd et al. (2007) rather than directly from mepolizumab trial data. The ERG suggested incorporating the average length of exacerbations measured in the MENSA trial, and the committee considered this appropriate.
- The model included different utility values in the 'on' and 'off' treatment health states, and so it captured more quality-of-life benefits than from just reducing exacerbations. The committee heard from the clinical experts that mepolizumab was unlikely to have an effect on symptoms. The company disagreed, but was unable to provide any evidence that mepolizumab is associated with an impact on symptoms over and above a reduction in exacerbations. The committee concluded that an on-treatment utility gain was inappropriate.

Overall the committee concluded that the health-related quality-of-life gain associated with mepolizumab was likely to be overestimated in the model.

4.24 The committee discussed the mortality rates in the model. It was aware that the company used the Watson et al. (2007) study for mortality from exacerbations resulting in hospitalisations. The committee understood that age affects the risk of asthma-related mortality and that the Watson et al. study included a constant rate of asthma-related mortality for people aged 45 years and older. It agreed with the ERG that stratifying mortality into narrower age bands, including having a different rate for 65 years and above, as in the study by Roberts et al. (2013), gave a more plausible measure of asthma-related mortality. The ERG highlighted that the rate of asthma-related mortality in Roberts et al. was about 6 times higher in the 65-years-and-above group than in the 45–54-years group. The committee noted the company's comment that background mortality in the model was age-adjusted and that it was not appropriate to age adjust asthma-related mortality because it considered that the mortality rate following an exacerbation was not dependent on age. The committee however agreed with the ERG that asthma-related mortality rises with age. The committee

concluded that the ERG's preferred approach of estimating asthma-related mortality from Roberts et al. was appropriate.

4.25 The committee noted that the mean age for patients in the model was 50.1 years. 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 incremental cost-effectiveness ratio (ICER). The clinical experts stated that 30 years was younger than the people that they saw in clinical practice in the UK. 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. After consultation, the company presented data from the British Thoracic Society, a cross sectional registry and a historical cohort study citing average ages of 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. Because the committee recognised that the relationship between age and mortality is not linear, it also recognised that the starting age was an important driver of the model. The committee was aware that in NICE's technology appraisal guidance on [omalizumab for asthma](#), the results presented were based on a weighted average of the ICERs for different age cohorts to reflect differing mortality risk by age. The committee therefore considered that variability in the age of starting mepolizumab should have been explored when estimating the ICER. The ERG explored this after consultation, and the committee noted that the impact on the ICER was marginal. The committee concluded that the age in the model was likely to be older than seen in clinical practice, but adjusting for this did not have a large impact on the ICER.

4.26 The committee considered the company's cost-effectiveness results in the population on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year (analysis 3). It noted that the base-case

ICER estimated by the company for mepolizumab compared with standard care was £22,100 per quality-adjusted life year (QALY) gained. It also noted the ERG's exploratory analyses that incorporated the committee's preferences (see sections 4.18–4.24):

- removing the additional utility gain for being on treatment
- incorporating age-related asthma mortality
- age-adjusting values of utilities
- assuming a lifetime duration of treatment
- sourcing the average duration of exacerbations from the MENSA trial
- setting the exacerbation rates for patients treated with mepolizumab who met the criteria to continue to those seen for the same patients in the COSMOS study.

The committee noted that these amendments resulted in an ICER of £59,900 per QALY gained. It noted that using direct EQ-5D values from the DREAM trial reduced this to £51,000 per QALY gained. The committee recognised that assuming a mean age lower than 50.1 years, and a waning effect of duration of response to treatment, was likely to increase the ICER (see sections 4.22 and 4.26). The committee concluded that the ICERs for mepolizumab compared with standard care were considerably above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

4.27 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 in this appraisal. It therefore concluded that the PPRS payment mechanism was not

relevant in considering the cost effectiveness of the technology in this appraisal.

4.28 The committee heard from stakeholders that mepolizumab is innovative 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, 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. The committee noted that the impact on the ICERs was negligible and heard from the ERG and the company that there were limitations in the analysis. The committee agreed that some benefits related to avoiding the significant adverse effects of oral 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 the QALY measure. The committee therefore agreed that mepolizumab could be considered innovative.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title: mepolizumab for treating severe refractory eosinophilic asthma	Section
Key conclusion		
	Mepolizumab is not recommended within its marketing authorisation as an add-on for treating severe refractory eosinophilic asthma.	1.1
	The committee concluded that, compared with placebo, mepolizumab is effective in reducing the rate of clinically significant exacerbations.	4.9
	The committee concluded that it could not consider the comparison between mepolizumab and omalizumab, because the meta-analyses were not sufficiently robust for decision-making. In addition, its guidance would not apply to asthma that has previously been treated	4.10

<p>with omalizumab because evidence for this position in the treatment pathway was not presented.</p> <p>The committee noted several definitions of the appropriate population put forward by the company and other stakeholders. The committee concluded that people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:</p> <ul style="list-style-type: none"> • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids <p>would best reflect the population seen in UK clinical practice. The committee considered the company's cost-effectiveness results in this population. It noted that, taking into account its preferred assumptions, the most plausible incremental cost-effectiveness ratio (ICER) was above £51,000 per quality-adjusted life year (QALY) gained.</p>		<p>4.7, 4.26</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>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 but there are long-term complications and they do not prevent exacerbations occurring. Patients would welcome treatment options that replace the need for corticosteroids.</p>	<p>4.1</p>
<p>The technology</p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee heard from clinical experts that mepolizumab is a novel treatment that reduces exacerbations and offers the potential to reduce corticosteroid use.</p>	<p>4.28</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee understood that people with uncontrolled severe refractory eosinophilic asthma having treatment according to step 4 or 5 of the British Thoracic Society and Scottish Intercollegiate guidelines, and having maintenance corticosteroids, would be considered eligible for treatment with mepolizumab.</p>	<p>3.1, 4.2</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>2.2</p>
<p>Evidence for clinical effectiveness</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 an indirect treatment comparison. The trials included different patient populations, including differences in disease severity. The committee concluded that the results from the company's indirect comparison of mepolizumab with omalizumab were highly uncertain and not suitable for decision-making.</p>	<p>4.9</p> <p>4.10</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee noted that people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:</p> <ul style="list-style-type: none"> • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids <p>would best reflect the population seen in UK clinical practice.</p>	<p>4.7</p>
<p>Uncertainties generated by the evidence</p>	<p>The committee concluded that the results from the company's indirect comparison of mepolizumab with omalizumab were highly uncertain and not suitable for decision-making.</p> <p>Different definitions for the appropriate population were put forward by the company and other stakeholders. There was substantial</p>	<p>4.10</p> <p>4.4 to</p>

	discussion about the appropriate thresholds for blood eosinophil count, number of exacerbations and dependency on maintenance oral corticosteroids.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	<p>The committee noted that people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:</p> <ul style="list-style-type: none"> • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids <p>would best reflect the population seen in UK clinical practice.</p>	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that, compared with placebo, mepolizumab was effective in reducing the rate of clinically significant exacerbations.	4.9
Evidence for cost effectiveness		
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.	3.21

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee concluded that assumptions about the continuation criteria and attrition rate in the model were associated with considerable uncertainty.</p> <p>The committee concluded that it would be mindful that accounting for waning would increase the ICER.</p> <p>The committee concluded that the health-related quality-of-life benefits of mepolizumab may be over-estimated in the model.</p> <p>The exacerbation rates in the model were uncertain.</p>	<p>4.15</p> <p>4.21</p> <p>4.23</p> <p>4.16 to 4.19</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>The committee concluded that direct EQ-5D values were preferable to mapped values.</p> <p>The committee concluded that the model over-estimated the health-related quality-of-life benefit associated with mepolizumab.</p> <p>The committee recognised that some benefits of reducing oral corticosteroids were not accounted for in the model, nor were the quality-of-life benefits to carers.</p>	<p>4.22</p> <p>4.23</p> <p>4.28</p>

<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee noted that people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:</p> <ul style="list-style-type: none"> • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids <p>would best reflect the population seen in UK clinical practice.</p>	<p>4.7</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>Exacerbation rates, age-related mortality estimates and attrition rates.</p>	<p>4.17, 4.21</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>£51,100 per QALY gained for mepolizumab compared with standard care.</p> <p>The committee noted that accounting for further uncertainties was likely to increase the ICER further.</p>	<p>4.26</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The company has agreed a patient access scheme with the Department of Health. If mepolizumab had been recommended, this scheme would provide a simple discount to the list price of mepolizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.</p>	<p>2.3</p>

End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equalities issues were identified.	

5 Related NICE guidance

Further information is available on the [NICE website](#).

- [Omalizumab for treating severe persistent allergic asthma](#) (2013) NICE technology appraisal guidance TA278
- [Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over](#) (2008) NICE technology appraisal TA138.

6 Proposed date for review of guidance

6.1 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.

Dr Amanda Adler
 Chair, appraisal committee
 April 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.

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.

Helen Tucker

Technical lead

Raisa Sidhu

Technical adviser

Jeremy Powell

Project manager

ISBN: