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 (see section 7) 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: 25 April 2015

Second appraisal committee meeting: 5 May 2016

Details of membership of the appraisal committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

1 Recommendations

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

1.2 People whose treatment with mepolizumab was started within the NHS before this guidance was published should be able to continue treatment 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 a type of white blood cell 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 for mepolizumab 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, 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; section 8). 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 a 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 steroid 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 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 oral corticosteroids and a

history of 2 or more exacerbations in the previous 12 months. All people in the trial had a blood eosinophil level (a type of white blood cell) of either 300 cells/microlitre or more in the 12 months before screening or 150 cells/microlitre or more at screening. The eosinophil count is a blood test that measures the concentration of eosinophils in the blood.

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 oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months. 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 injectable) 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 reduction 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 need patients to 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 results for 3 populations, which are described below and summarised in table 3. The company presented a modified intention-to-treat (ITT), that is, all trial patients who were randomised and had at least 1 dose of study medication. The company also analysed mepolizumab's effect on the rate of exacerbations that needed hospitalisation or emergency department visits. The company presented results to show that subgroups with more severe disease were likely to benefit more from treatment with mepolizumab than patients with less severe disease. To identify the most severe patients and those with the greatest treatment response, and define subgroups, the company considered: sex; age; weight; region; baseline percentage predicted forced expiratory volume in 1 second ($FEV_{1)}$; airway reversibility; number of exacerbations in the previous 12 months; baseline blood eosinophil count; baseline use of maintenance oral corticosteroids; and IgE level. Subgroup analyses used data from DREAM and MENSA. The company stated that baseline blood eosinophil count most strongly predicted treatment response. For people with a blood eosinophil count of 150 cells/microlitre or more when starting treatment, the post hoc modelling of the modified ITT population of the DREAM trial patients randomised to mepolizumab had a lower rate (reduced by 30% or more) of exacerbations than people randomised to placebo; the same value for the MENSA trial was 39%. Additional predictive modelling showed 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 exacerbations (fewer than 4).

3.8 Based on these results, 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 that although all patients in the trials are likely to benefit from mepolizumab irrespective of eosinophil levels, the benefits will be greater in the company's chosen subgroup and will ensure an efficient use of NHS resources.

3.9 The company stated that people who have systemic corticosteroids represent a population with very severe disease and so should be considered regardless of the number of exacerbations they have had in the previous 12 months. The company highlighted the benefits of reducing corticosteroid exposure, which it considered were not fully captured in its clinical- and cost-effectiveness analyses. But, the company presented further analyses that excluded the systemic corticosteroid criteria from the 'proposed population' (hereafter referred to as the 'restricted population'). So, this population included:

- adults with a blood eosinophil count of 150 cells/microliter 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 the group that were included in the proposed population, but 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

Table 3 Proposed populations: mepolizumab compared with standard care

Criteria			Modified intention-to-treat population	Proposed population	Restricted population	ERG requested population
OR	Blood eosinophil count of more than 300 eosinophils cells/microlitre in the previous 12 months		✓	-	-	-
	Blood eosinophil count of 150 or more cells/microlitre when starting treatment		✓	✓	✓	✓
AND						
OR	Fewer than 4 exacerbations	Not having systemic corticosteroids	✓	X	X	X
		Having systemic corticosteroids	✓	✓	X	✓
	4 or more exacerbations	Not having systemic corticosteroids	✓	✓	✓	X
		Having systemic corticosteroids	✓	✓	✓	X

Abbreviation: ERG, evidence review group.
✓ included; X excluded; - not considered

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)**	**Proposed 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 (100 mg SC)	0.68 (0.47 to 0.99; p value 0.042)	0.77 (0.51 to 1.17; p value 0.222)	0.81 (0.40 to 1.64; p value 0.556)
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. None of these results were statistically significant.

3.12 The company acknowledged that the populations presented may not be powered to find that mepolizumab reduces the occurrence of rarer events, for example, exacerbations needing hospitalisation, but stated that the trend 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 mean change from baseline EQ-5D score at

week 52 was 0.07 for placebo and 0.08 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, which it considered did not reflect the impact of severe asthma on quality of life and also meant that for this group of patients, quality of life could not improve with mepolizumab treatment. 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 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 modified ITT population. The company stated this suggested that EQ-5D is not an appropriate measure in severe asthma.

3.14 The MENSA and SIRIUS trials included the St George's Respiratory Questionnaire, a disease-specific questionnaire designed to measure health impairment in patients with asthma, which showed that mepolizumab improved quality of life compared with placebo. The company stated that the minimal clinically important difference for St George's Respiratory Questionnaire is 4 units and the differences in MENSA and SIRIUS range from 5 to 13 units for all 3 populations (see section 3.23). The company noted that reductions in quality of life during an exacerbation and fear of an exacerbation would not have been captured in these estimates.

3.15 The trials also included 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 FEV_1. 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 was based on a population that was eligible for mepolizumab (based on 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 patients should have had 2 or more systemic exacerbations needing treatment with systemic corticosteroids 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 omalizumab for treating severe persistent allergic asthma stipulates that patients should have 2 or more exacerbations needing treatment with systemic corticosteroids in the previous year. So, the trial

data for omalizumab was from a less severe population that would be treated in clinical practice. It also included some patients that 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 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).

3.21 The company also presented data on adverse events for mepolizumab 100 mg subcutaneous from the COSMOS and COLUMBA studies. In both studies the most frequent adverse events were nasopharyngitis, upper respiratory tract infection, headache, and injection site reactions.

Cost effectiveness

3.22 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 and table 3):

- 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 rather than in its proposed population because it did not have access to patient-level data for omalizumab (section 3.17).

3.23 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

3.24 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 if taking mepolizumab and at 16 weeks if taking omalizumab. Patients moved to the 'on treatment

post-continuation assessment' state if they met the criteria to continue treatment. The criterion to continue treatment was that there must be no increase in the number of exacerbations from baseline. If not met, patients entered the 'off treatment' state in which they had standard care and they stayed there until death. Otherwise, patients move to the 'on treatment post-continuation assessment' state and stay there until they stopped treatment or died. In its base case, the company assumed that 10% of patients stop treatment every year and no patients are treated for longer than 10 years. The company assumed that there was a constant treatment benefit for mepolizumab over time. During each cycle, patients in any health state (except death), may 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 effect of exacerbations on utility, risk of death, and cost was taken into account.

3.25 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. For the first year of the model, until patients have an assessment at 12 months to decide if treatment should continue, the company assumed that people on mepolizumab have the mean treatment effect that people randomised to mepolizumab in MENSA had at 32 weeks. After 12 months, people were divided into one of 2 groups. For patients who meet the criteria to continue treatment beyond 12 months, the company used the MENSA rates observed between 16 and 32 weeks, for people whose condition responded to mepolizumab at 32 weeks. Patients who do not meet the criteria to continue, get standard care and

have the same exacerbation rates as the standard care group, based on the exacerbation rate of the placebo group from MENSA.

3.26 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.

3.27 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.

3.28 The company got utility values for mepolizumab by mapping St George's Respiratory Questionnaire 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

	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.

3.29 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).

3.30 In the company's base case for the modified ITT population, 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.

3.31 In response to the request from the ERG (section 3.9), the company presented results for people with:

- 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 to 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.

3.32 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.

3.33 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 6 adverse events associated with systemic corticosteroid therapy: myocardial infarction; glaucoma; 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 results of 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. In SIRIUS at 24 weeks, patients in the mepolizumab group had reduced their daily maintenance oral corticosteroids by a median of 30%. The company also 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 the SIRIUS trial). Results based on both approaches had little effect on the ICERs.

ERG comments

3.34 The ERG stated that the post-hoc modelling analysis to identify the company's 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/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/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/microlitre or more threshold may be because of chance or confounding.

3.35 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 maintenance dose) or
- hospitalisation or
- hospital emergency department visits.

3.36 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, a random-effects model would be more appropriate than a fixed-effect model for all scenarios and endpoints.

3.37 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 anti-mepolizumab antibodies, but the company stated that this did not affect the pharmacokinetics and pharmacodynamics of mepolizumab in most patients.

3.38 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.

3.39 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 requested 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.

3.40 The ERG noted that patients who do not continue mepolizumab have the same rates of exacerbation as patients in the standard-care group in the model. 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.

3.41 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.

3.42 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.

3.43 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 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.

3.44 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 study. The ERG explained that the Watson et al. (2007) 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.

3.45 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.

3.46 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 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.

3.47 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 more than 300 cells/microlitre 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 not one 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.

3.48 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 scenario analyses by the ERG for mepolizumab compared with standard care (includes PAS 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
Exacerbations 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.			

3.49 The ERG compared mepolizumab with omalizumab, with the patient access schemes applied for both drugs. This used the modified ITT

population for mepolizumab and the full trial population for omalizumab (see section 3.17). The ERG also applied the 5 changes to the company's model listed in table 5, which resulted in omalizumab being dominated (omalizumab more costly and less effective) by mepolizumab. The ERG also carried out the following scenario analyses:

- using the assumed annual cost of omalizumab reported in the NICE technology appraisal guidance on omalizumab
- using the exacerbation rates ratios based on people on maintenance oral corticosteroids from the SIRIUS study
- using the results of the network meta-analysis random-effects model.

Combining all the ERG's exploratory analyses reversed the results and mepolizumab was dominated by omalizumab (mepolizumab more costly and less effective).

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 people 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 of severe asthma. The committee heard from clinical experts that standard

treatment for severe refractory eosinophilic asthma is oral systemic corticosteroids. The committee heard that patients' disease characteristically responds rapidly to oral systemic corticosteroids but these are associated with several 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 have a significant impact on patients. So patients particularly welcome treatment options that replace the need for corticosteroids. The committee heard that treatments such as mepolizumab reduce 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 treatment options.

4.2 The committee heard from clinical experts that treatment for asthma in clinical practice followed guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network 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 oral systemic corticosteroids could be used for short periods, for example to manage an exacerbation, or 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. The clinical experts stated that the term 'refractory' was not used in practice and no specific definition was available. The committee understood that people with uncontrolled severe refractory

eosinophilic asthma having treatment described in steps 4 and 5 of the guidelines could be considered eligible for 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, but then use objective criteria in the form of evidence of eosinophilia (either peripherally in the blood, from induced sputum, exhaled nitric oxide levels or biopsy specimens from nasal polyps) to confirm the diagnosis. Factors such as a rapid response to oral corticosteroids are also used to diagnose eosinophilic asthma. The committee heard that peripheral blood eosinophil count was a commonly used biomarker, but that it cannot be used on its own because it can be suppressed by corticosteroid use. The clinical experts stated that measuring sputum eosinophilia gives the most accurate diagnosis of eosinophilic asthma, but this is not widely used in clinical practice because it is very resource intensive. The committee acknowledged the complexity of diagnosing eosinophilic asthma.

4.4 The committee discussed the appropriate population for the appraisal. It recognised the company had presented 3 different populations that were defined by eosinophilia count; frequency of exacerbations; and whether or not patients were treated with maintenance oral corticosteroids. The Committee noted the NICE methods guide which states that when considering subgroup analyses, the Appraisal Committee will take specific note of the biological or clinical plausibility of a subgroup effect in addition to the strength of the evidence in favour of such an effect. The committee first discussed the eosinophilia criterion (see section 3.46 for exacerbation frequency and section 3.45 for corticosteroid use). The committee noted that the populations in MENSA and SIRIUS included people with a blood eosinophil count of more than 300 cells/microlitre in the previous 12 months, or 150 cells/microlitre or more when starting treatment. The committee was aware that 2 of the company's proposed populations only

included the blood eosinophil count of 150 cells/microlitre or more when starting treatment criterion (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 was used, a threshold of 300 cells/microlitre or more was more reflective of clinical practice.
- Explanation from clinical experts that eosinophil levels fluctuate and systemic corticosteroid treatment suppresses blood eosinophil levels, meaning this measure is not reliable.
- 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 propose a blood eosinophil count of 150 cells/microlitre or more as a diagnostic measure when starting treatment, but rather chose this group because the results looked more effective, and to improve cost effectiveness.
- The evidence review group (ERG) comment that in the company's analysis, the reduction in exacerbations with mepolizumab was greater in people with a blood eosinophil count below 300 cells/microlitre compared with those with 300 cells/microlitre or more. The clinical experts stated that this was counterintuitive.

The committee noted that any subgroup analysis should be based on clinical plausibility and agreed that a population based on a threshold of 150 cells or more/microlitre when starting treatment was not relevant to clinical practice. The committee concluded that including this criterion to define a subpopulation was not appropriate.

4.5 The committee next considered the frequency of exacerbations applied to the proposed and restricted populations. The committee noted that

MENSA and DREAM recruited people with 2 or more exacerbations in the previous year. The committee was aware that the company's proposed and restricted populations included a criterion for people with 4 or more exacerbations per year. The committee heard from the clinical experts that this was inappropriate because clinicians would want to offer mepolizumab to patients who have 2 or more exacerbations per year, especially for people receiving maintenance systemic corticosteroids. The Committee also recognised that because exacerbations are infrequent events, event rates would vary between one year and the next, so defining a criterion on a specific value, may not be reliable (that is, the same patient may experience 3 exacerbations one year, and 4 the next). The committee concluded that a criterion based on 4 exacerbations was not clinically appropriate.

4.6 The committee then 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 Scottish Intercollegiate Guidelines Network guidelines, who may not be on 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 committee considered the clinical experts' statements that maintenance systemic corticosteroids is an effective treatment for people with severe asthma, and that people who are receiving maintenance corticosteroids will have severe refractory disease. The committee concluded that a criterion reflecting maintenance corticosteroid to define a subpopulation was clinically appropriate. The Committee concluded that it's preferred population, taking into account the population on the trials, includes:

- a blood eosinophil count of 300 or more cells/microlitre in the previous year or 150 or more cells/microlitre when starting treatment; and
- 2 or more exacerbations in the previous year; and
- dependency on maintenance oral corticosteroids.

4.7 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.

4.8 The committee considered the results from the key trials: MENSA, DREAM and SIRIUS. The committee noted that the company presented results for 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 and not statistically significant 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 considered that people on maintenance oral corticosteroids, in whom best standard of care had been maximised, were most likely to have treatment with

mepolizumab (see section 4.6) and that an aim of treatment in clinical practice would be to reduce oral corticosteroid use. So, it agreed that the SIRIUS trial may be more generalisable to clinical practice than MENSA and DREAM. The committee heard from clinical experts that mepolizumab was 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 was effective in reducing the rate of clinically significant exacerbations.

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 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, but, because only 2 trials were included in each arm of the network meta-analysis, considered that estimating heterogeneity was difficult and 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 agreed that there are few patients who clinicians would consider equally likely to have either drug. The committee therefore did not consider this comparison further.

4.10 The committee recognised that no data had been presented for using mepolizumab after omalizumab. It concluded that in the absence of data, mepolizumab could not be considered at this stage in the pathway and its guidance for mepolizumab would not apply to people previously treated with omalizumab.

Cost effectiveness

4.11 The committee noted that, to compare mepolizumab with standard care, the company presented cost-effectiveness results based on 3 populations: the modified ITT population; the company's proposed population; and the company's proposed restricted population (see table 3). The committee recalled its previous conclusion that none of these populations reflected severe refractory disease, but agreed that the modified ITT population best reflected patients seen in clinical practice in the UK. The committee remained concerned that this population included people who were not having maintenance corticosteroids. The committee also noted that the company presented cost-effectiveness analyses comparing mepolizumab with omalizumab. The committee was aware that this was underpinned by

the results from company's indirect comparison and recalled its previous conclusion that these results were highly uncertain and not suitable for decision-making. The committee concluded that it would consider the company's analyses for mepolizumab compared with standard care using the modified ITT population.

4.12 The committee discussed the choice of standard care as a comparator in the company's model. 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 patients may already be having maintenance oral corticosteroids and one of the aims of mepolizumab treatment is to reduce use of maintenance corticosteroids and therefore it was not an appropriate comparator. The committee agreed with the ERG that maintenance oral corticosteroids in addition to standard care was an appropriate comparator for patients not currently having maintenance corticosteroids and noted that it had not been presented with this comparison. However, the committee recalled its previous conclusion that it would consider the appropriate population for decision-making to be people who were on maintenance oral corticosteroids (see section 4.6). The committee was satisfied that for the people on maintenance oral corticosteroids, standard care including oral corticosteroids in short courses was an appropriate comparator.

4.13 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 patients are reviewed at least once a year. 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 patients remain stable, that is they have fewer or the same number of exacerbations than in the previous year, because exacerbations may remain stable in patients 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 considered that a 10% attrition rate seemed to be arbitrary and did not constitute a formal continuation rule. The Committee concluded that analyses to explore the sensitivity of cost-effectiveness to the attrition rate would have been valuable.

4.14 The committee heard from the ERG that patients who do not meet the criteria to continue treatment with mepolizumab were assumed to have the same rate of exacerbations as patients in the standard-care group who had never had mepolizumab. The committee heard from the clinical experts that this assumption cannot be generalised to all patients. The committee agreed with the ERG that this was likely to underestimate the exacerbation rates for some patients and increase the ICER. The committee was also aware of the company's assumption that, after stopping mepolizumab, whether or not their disease has a history of responding to it, 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 whose disease had not responded and so, this was an unrealistic assumption. The committee concluded that assumptions around exacerbation rates in the model were associated with considerable uncertainty and that more plausible exacerbation rates should be explored.

4.15 The committee was aware that the company used data for exacerbation rates from the MENSA trial in the model. The committee noted the ERG comments that exacerbation rates in the MENSA trial were measured shortly after patients started treatment and so, 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 patients meeting the continuation criteria because the study measured exacerbation rates for a full year in people who had already been on mepolizumab for 32 weeks. The committee was aware that COSMOS also included people from the SIRIUS trial, which represented a different patient population. The committee was also concerned that the data from COSMOS had not been used for the standard care arm, and the ERG explained that the data to allow for this were not presented by the company. The committee acknowledged the limitations of incorporating data from the MENSA trial, and considered that the inclusion of data from COSMOS was preferable, but it was important to separate out the underlying rate of exacerbations with standard care and the relative effect of mepolizumab.

4.16 The committee discussed the duration of treatment and duration of response with mepolizumab assumed by the company 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 lifetime treatment duration was more appropriate. The committee heard from the clinical experts that they would treat patients for as long as the patients benefited. The clinical experts stated that they would expect that disease that responded would 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 lifetime duration of mepolizumab and concluded that this was appropriate (noting this marginally increased the ICER). The committee also considered that a scenario exploring a waning effect of mepolizumab would be valuable.

4.17 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 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 the company's justification that the St George's Respiratory Questionnaire 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 committee concluded that direct EQ-5D values were preferable.

4.18 The committee further considered the utilities in the model, it noted:

- That the utilities had not been adjusted for age, and heard from the ERG that this would slightly increase the ICER. 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 overestimate utility with mepolizumab.
- The company assumed each exacerbation lasted 28 days, which came from Lloyd et al. (2007) rather than 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 further quality of life benefits than reducing exacerbations. It heard from the clinical experts that mepolizumab was unlikely to have an effect on symptoms. So, the committee concluded that this 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.

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

4.20 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 England. The committee agreed that UK registry data or other observational data would help provide the age distribution of patients in clinical practice and validate the model. The committee recognised that the relationship between age and mortality is not linear (see section 4.19), which meant 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 age of starting mepolizumab should have been explored in estimating the ICER. The committee concluded

that the age in the model was likely to be older than seen in clinical practice, and adjusting for this would increase the ICER.

4.21 The committee considered the company's cost-effectiveness results. The committee appreciated it was not presented with results for its preferred subpopulation, that is:

- not limited by blood eosinophilia count,
- more than 2 exacerbations in the previous year, and
- limited to refractory patients having maintenance corticosteroids.

The committee considered the population most close to this to be the modified ITT population. It considered the cost effectiveness results for this population, noting they all included the patient access scheme price for mepolizumab. It noted that the base-case probabilistic ICER estimated by the company for mepolizumab compared with standard care was £31,700 per quality-adjusted life year (QALY) gained. It also noted that the ERG presented exploratory analyses incorporating the committee's preferences:

- direct EQ-5D scores (see section 4.17);
- age-related asthma mortality (see section 4.19);
- lifetime treatment duration (see section 4.16);
- disutilities based on the average duration of exacerbations from the MENSA trial (see section 4.18); and
- setting the exacerbation rates for those meeting the continuation criteria to those seen in the COSMOS study (see section 4.15).

The committee noted that these amendments resulted in an ICER of £72,500 per QALY gained. The committee noted that adjusting the utilities for age and assuming a mean age lower than 50.1 years in the model was likely to increase the ICER further (see sections 4.13 and 4.19). The committee was also aware that several uncertainties remained, such as:

- the continuation criteria in the model (see section 4.14)
- waning effect of mepolizumab (see section 4.16)
- potential overestimation of utilities from having different utility values for the on and off treatment health states (see section 4.18)
- when incorporating exacerbation rates from the COSMOS trial for mepolizumab, similar amendments were not made to the standard care arm (see section 4.15)
- the ICERs did not take into account the possibility that the age of patients in England differs from the trials (see section 4.20).

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).

4.22 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.

4.23 The committee heard from stakeholders that mepolizumab was innovative in its potential to make a significant and substantial impact on health-related benefits. The committee heard from clinical experts that mepolizumab was a novel treatment with the potential to reduce corticosteroid use. The committee noted that it had not seen any evidence on preventing or delaying maintenance oral corticosteroids but heard from the clinicians that this was an important aim of treatment with

mepolizumab. 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. The committee therefore agreed that mepolizumab could be considered innovative.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Mepolizumab is not recommended within its marketing authorisation for treating severe refractory eosinophilic asthma, that is, as an add-on treatment for severe refractory eosinophilic asthma in adults. People whose treatment with mepolizumab was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. The committee concluded that, compared with placebo, mepolizumab was effective in reducing the rate of clinically significant exacerbations. The committee concluded that it could not consider the comparison between mepolizumab and omalizumab, as the meta-analyses were not sufficiently robust for decision making. It addition, and its guidance would not apply to people previously treated with		1.1 1.2 4.8

omalizumab as evidence at this position in the pathway was not presented. The company presented 2 sub-populations defined by eosinophil levels, exacerbation rates and oral corticosteroid use. The Committee agreed that the population most relevant to clinical practice included those who were receiving maintenance oral corticosteroids, irrespective of eosinophil levels or exacerbation rates. The modified intention-to-treat (ITT) population was used for decision making. The company's ICER for mepolizumab compared with standard care, (including the patient access scheme price for mepolizumab) was £31,700 per quality-adjusted life-year (QALY) gained. ERG exploratory analyses incorporating the committee's preferences had an ICER of £72,500 per QALY gained. The Committee noted further uncertainties that would increase the ICER. The Committee agreed mepolizumab was innovative as its impact on the quality of life of carers, and the quality of life benefits of reducing oral corticosteroids were not captured in the model. The Committee agreed that accounting for this would reduce the ICER. 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).	4.9
Current practice	

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 happen without warning. The committee heard that standard treatment for severe refractory eosinophilic asthma is oral corticosteroids but there are several long-term complications and do not prevent exacerbations occurring. Patients welcome treatment options that replace the need for corticosteroids, and reduce the risk of exacerbations.	4.1
The technology		
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 was a novel treatment that reduced exacerbations offered the potential to reduce corticosteroid use. The committee noted that it had not seen any evidence preventing or delaying maintenance oral corticosteroids but heard from the clinicians that this was an important aim of treatment with mepolizumab.	4.23

What is the position of the treatment in the pathway of care for the condition?	The committee understood that people with uncontrolled severe refractory eosinophilic asthma receiving treatment according to Step 4 or 5 of the British Thoracic Society and Scottish Intercollegiate guidelines, and receiving maintenance corticosteroids would be considered eligible for treatment with mepolizumab.	4.2, 3.1
Adverse reactions	The summary of product characteristics lists headache as a very common adverse reactions for mepolizumab. Common adverse reactions 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.	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Evidence for mepolizumab compared with placebo came from 3 randomised controlled trials. Evidence for mepolizumab compared with omalizumab came from an indirect treatment comparison. The trials supporting each of the treatments included very different patient populations, including differences in disease severity. The committee concluded that the results from the company's indirect comparison of mepolizumab with omalizumab	4.8 4.9

	were highly uncertain and not suitable for decision-making.	

Relevance to general clinical practice in the NHS	The committee agreed that people on maintenance oral corticosteroids, in whom best standard of care had been maximised, were most likely to have treatment with mepolizumab.	4.8
Uncertainties generated by the evidence	The committee agreed that the mITT population best represented clinical practice; however there was uncertainty as this included people who were not taking maintenance corticosteroid. 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 also concluded that in the absence of data, its guidance for mepolizumab would not apply to people previously treated with omalizumab.	4.11 4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The company presented evidence for 2 subgroups defined by eosinophil level, exacerbation rate, and maintenance corticosteroid use. The Committee agreed that the eosinophil and exacerbation criteria proposed were not clinically relevant. The Committee agreed that the population who would receive mepolizumab would be those who were receiving maintenance corticosteroids.	4.4 - 4.6

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.	4.8
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, and compared with omalizumab.	3.21

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee agreed that there was uncertainty about whether the assumed age of patients at the start of treatment reflected clinical practice.	4.20
	The committee concluded that assumptions around the continuation criteria and attrition rate in the model were associated with considerable uncertainty.	4.14
	The committee considered that a scenario exploring a waning effect of mepolizumab would be valuable.	4.16
	The committee concluded that the quality-of-life benefits of mepolizumab may be over-estimated in the model.	4.18 4.19
	The long-term exacerbation rates associated with mepolizumab were uncertain.	4.20

Incorporation of health-related quality-of-life benefits and utility values 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 concluded that direct EQ-5D values were preferable than mapped values The committee concluded that the model over-estimated quality of life benefit associated with mepolizumab The committee recognised that the benefits of reducing oral corticosteroids were not accounted for in the model, nor were the quality of life benefits to carers.	4.19 4.20 4.23
Are there specific groups of people for whom the technology is particularly cost effective?	No. The company presented analyses for subgroups based on exacerbation rates and eosinophil cell count criteria. These Committee agreed these were not clinically relevant subgroups	4.4, 4.5
What are the key drivers of cost effectiveness?	Exacerbation rates, morality and utility values.	4.14, 4.18, 4.20

Most likely cost-effectiveness estimate (given as an ICER)	£72,500 per QALY for mepolizumab compared with standard care. The committee noted that accounting for further uncertainties was likely to increase the ICER further. The committee recognised that accounting for the benefits of reducing corticosteroid treatment would reduce the ICER.	4.21, 4.23
Additional factors taken into account		
Patient access schemes (PPRS)	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.	2.3
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, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Dr Mark Glover
MRC Clinician Scientist, Associate Professor and Honorary Consultant Physician

Dr Rebecca Kearney
Clinical Lecturer, University of Warwick

Dr Sanjay Kinra
Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy
Consultant, Public Health, Public Health Agency, Northern Ireland

Mr Christopher O'Regan
Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Nigel de Kare Silver

GP

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Mr Nigel Westwood

Lay member

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

8 Sources of evidence considered by the committee

A. The evidence review group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield:

- Stevenson M, Bermejo I, Cooper K et al., Mepolizumab for treating severe eosinophilic asthma: A single technology appraisal, February 2016

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- GlaxoSmithKline

II. Professional/expert and patient/carer groups:

- Asthma UK
- British Association of Dermatologists
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Novartis

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal

view on mepolizumab by attending the initial committee discussion and providing a written statement to the committee. They are invited to comment on the ACD.

- Dr Shuaib Nasser, Consultant Physician in Allergy and Asthma, Cambridge University Hospitals NHS Foundation Trust, nominated by the British Society of Allergy and Clinical Immunology– clinical expert
- Professor Andrew Wardlaw, Professor of Allergy and Respiratory Medicine, University of Leicester and University Hospitals of Leicester, nominated by the Royal College of Physicians – clinical expert
- Ms Lehanne Sergison, nominated by Asthma UK – patient expert

D. Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline