NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using reslizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.

- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using reslizumab 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: **5pm, Tuesday 6 December 2016**

Second appraisal committee meeting: **Wednesday 11 January 2017**

- Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 The committee is minded not to recommend reslizumab within its marketing authorisation, that is, as an add-on to standard therapy for treating severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment in adults.

1.2 The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include:

- the effect of reslizumab on exacerbations for subgroups of people with 3 or more or with 4 or more exacerbations in the previous year. These should not include an adjustment for a placebo effect. Any adjustment related to specific subgroups should be fully explained and justified
- appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion
- drug wastage using only the licensed 100-mg vial
- evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment)

- the individual and combined effects of all amendments on the incremental cost-effectiveness ratios (ICERs) for adults with inadequately controlled severe eosinophilic asthma despite optimised best standard care at specialist centres.
- the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.

2 The technology

Description of the technology	Reslizumab (Cinqaero, Teva) is an interleukin-5 inhibitor that reduces eosinophil numbers and activity.
Marketing authorisation	Reslizumab has a marketing authorisation in the UK as 'add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment'.
Adverse reactions	The most common adverse reaction is increased blood creatine phosphokinase, which is transient and asymptomatic. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Intravenous infusion of 3 mg/kg body weight once every 4 weeks.
Price	The anticipated list price provided in the company submission is £499.99 per 100-mg vial (excluding VAT). The company has agreed a patient access scheme with the Department of Health. If reslizumab had been recommended, this scheme would have provided a simple discount to the list price of reslizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Teva and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of reslizumab, having considered evidence on the nature of severe eosinophilic asthma inadequately controlled by inhaled corticosteroids and the value placed on the benefits of reslizumab by

people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Patient experience

4.1 The committee understood that inadequately controlled severe eosinophilic asthma is a distressing and socially isolating condition. It heard from the patient expert that severe asthma has an unpredictable course. People with very severe asthma are often unable to work and may need help with day-to-day activities because of the symptoms. Exacerbations are very frightening and can happen without warning. They can result in frequent hospital visits and in severe cases are life-threatening, needing intubation. The committee heard from the clinical experts that standard treatment for inadequately controlled severe eosinophilic asthma is corticosteroids. These are often effective, and oral or injected corticosteroids are the mainstay of treatment for exacerbations, but when taken frequently or long term they are associated with some major complications. The patient expert explained that these include diabetes, glaucoma, weight gain, bone density loss, hip replacement, raised blood pressure and mood swings. These can have a significant impact on patients, and can mean that numerous additional medications are needed to counteract the effects of the corticosteroids. The committee heard from the patient expert that she has to attend appointments for these complications, and it takes between 2 to 4 hours daily to administer all of her medicines. The committee understood that people would welcome treatment options that replace the need for, or reduce the dose of, oral corticosteroids. The committee heard that treatments such as reslizumab reduce the number of exacerbations, and are also anticipated to reduce oral corticosteroid use. It concluded that inadequately controlled severe eosinophilic asthma is associated with substantial morbidity and that there is a need for alternative treatment options.

Current clinical management of asthma

4.2 The committee heard from the clinical experts that treatment for asthma in clinical practice follows guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (see www.brit-thoracic.org.uk). The clinical experts explained that the management of severe eosinophilic asthma lies within what were previously known as step 4 and step 5 of the superseded 2014 version of these guidelines. The current guidelines (2016) indicate that people having high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) should be referred for specialist care. The clinical experts explained that the management of severe eosinophilic asthma lies within the high-dose therapies (previously step 4) or continuous or frequent use of oral steroids (previously step 5) stages of these guidelines. Additional therapies may include leukotriene receptor antagonists, theophyllines, oral corticosteroids, and help with smoking cessation. The committee understood that oral or injected corticosteroids can be used for short periods, for example to manage an exacerbation, but oral corticosteroids can be used as long-term maintenance. The committee was aware that the marketing authorisation for reslizumab is for 'severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment'. It questioned whether only people who continue to have exacerbations despite treatment with continuous or frequent use of oral steroids (previously step 5 of the guidelines) would be eligible for reslizumab. The clinical experts explained that people who have severe uncontrolled eosinophilic asthma having high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) would be treated at specialist centres, and that many of these patients have asthma that will respond to optimised treatment. Reslizumab would only be considered for patients who continue to have clinically significant exacerbations despite optimised conventional treatment, and

approximately 50% of these people might be taking maintenance oral corticosteroids. The committee understood that people with severe eosinophilic asthma on optimised treatment described in the high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) stages of the guidelines would be considered eligible for treatment with reslizumab.

Diagnosing severe eosinophilic asthma

4.3 The committee heard from the clinical experts that there are no standard diagnostic criteria for severe eosinophilic asthma in clinical practice. It heard that clinicians use the patient's phenotype to come to a probable diagnosis, which is confirmed using objective criteria in the form of evidence of eosinophilia (including blood or sputum eosinophil counts, exhaled nitric oxide levels, or biopsy specimens from nasal polyps). A rapid response to oral corticosteroids is also used to diagnose eosinophilic asthma. The committee heard that peripheral blood eosinophil count is a commonly used biomarker but it is suppressed by corticosteroid use, therefore only measurements taken before corticosteroid treatment are reliable. 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. The committee acknowledged the complexity of diagnosing eosinophilic asthma.

Clinical effectiveness

Population

4.4 The committee discussed the generalisability of the clinical trials to UK clinical practice. The company presented evidence from trials that included people aged 12 to 75 years with asthma and a blood eosinophil count of 400 cells/microlitre or more, inadequately controlled with medium to high-dose inhaled corticosteroids. The committee noted that the key

trials, study 3082 and study 3083, included people with a blood eosinophil count of more than 400 cells/microlitre in the previous 12 months. The committee was aware that the marketing authorisation for reslizumab does not specify a specific eosinophil count because the European Medicines Agency stated that blood eosinophil levels are not sufficiently predictive to include a cut-off value. The clinical experts stated that the high eosinophil count threshold was a limitation of the clinical trials because reslizumab is more effective the higher the eosinophil count, and therefore it might not be as effective in clinical practice as in the trials. They also explained that some patients in the trials may have had sensitivity to fungal allergens, which would account for the high eosinophil counts observed at baseline. However, the clinical experts clarified that people with lower eosinophil counts than those in the trials may also potentially benefit from treatment with reslizumab. The committee noted that a small proportion of patients in the trials were taking oral corticosteroids, but they were not permitted to reduce their corticosteroid dose during the trial. The committee concluded that the studies are relevant to the UK but that, in clinical practice, patients considered for this treatment may have lower eosinophil counts than in the trials and a higher percentage will be on oral corticosteroids.

Frequency of exacerbations

4.5 The committee noted that study 3082 and study 3083 recruited people with 1 or more exacerbations in the previous year. It was aware that the company proposed, and presented a base case cost-effectiveness analysis for, a restricted population including people with 3 or more exacerbations per year. The committee heard from the clinical experts that they would particularly like to have this treatment available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year. However, the committee also heard that the number of exacerbations in one year is not necessarily indicative of future

exacerbation rates, and that event rates vary in patients from year to year. It considered that this is a limitation of the trials, which looked at only one year in what is a variable and lifelong condition. The committee concluded that a criterion based on the number of exacerbations was not unreasonable, and expressed the view that the more frequent the exacerbations, the greater the clinical need.

4.6 The committee discussed whether treatment with reslizumab would be appropriate for people who do not take maintenance oral corticosteroids. The clinical experts highlighted that probably at least 50% of patients on what were previously known as steps 4 or 5 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network guidelines (see www.brit-thoracic.org.uk) are being treated with maintenance oral corticosteroids, but still have several exacerbations. The clinical experts explained that these people would be eligible for treatment with reslizumab but there are also other patients, who are not taking maintenance oral corticosteroids, who would benefit from reslizumab treatment. Patients who are not being treated with maintenance oral corticosteroids may receive one of the following maintenance treatments in addition to high-dose inhaled corticosteroids: leukotriene receptor antagonists, theophylline, slow-release beta-2 agonists or tiotropium. The committee considered the clinical experts' statements that maintenance corticosteroids are an effective treatment for people with severe asthma, and that a proportion of people who are taking maintenance corticosteroids will still have uncontrolled severe eosinophilic asthma. The committee noted that there are limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19% and 12% of people respectively in study 3082 and study 3083 fulfilled this criterion. However the committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.

Direct comparison with best supportive care

4.7 The committee considered the results from the trials, including study 3082 and study 3083. It noted that reslizumab, compared with placebo, was associated with lower rates of clinically significant exacerbations. The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.

Indirect treatment comparison with omalizumab

4.8 The committee noted that the NICE scope included omalizumab as a comparator in a small 'overlap' population of people who also had severe persistent allergic IgE-mediated asthma, and therefore could have either reslizumab or omalizumab. It heard that clinicians would decide which drug is most appropriate based on the person's phenotype. For predominantly eosinophilic symptoms, such as nasal polyps and sinusitis, people would be offered reslizumab. People with predominantly IgE related symptoms, such as eczema and urticaria, would be offered omalizumab. The committee noted that the company had presented an indirect treatment comparison using data from study 3082 and study 3083 for reslizumab and from the INNOVATE and EXTRA trials for omalizumab. It noted that the company based its comparison on the full trial populations, but there are fundamental differences between them. The committee acknowledged that the 2 drugs have different mechanisms of action and different populations. It also considered that adjusting for these differences in the very small overlap population was unlikely to be robust. The committee concluded that the results from the company's indirect comparison of reslizumab with omalizumab were highly uncertain and not suitable for decision-making. The committee therefore did not consider this comparison further.

Cost effectiveness

4.9 The committee considered the company's cost-effectiveness analysis. It noted that the company's base case was for reslizumab compared with standard care, for people with severe asthma who have had 3 or more exacerbations in the previous year. The committee noted that this is a subgroup of the overall trial population of people with severe asthma who have had 1 or more exacerbations in the previous year. The committee recalled its previous conclusion (see section 4.4) that neither the trials, nor the base-case populations, accurately reflect patients in the UK who might be considered for reslizumab; people with severe disease despite optimised care, often with lower eosinophil counts than in the trials, and with higher rates of maintenance corticosteroid use. The committee noted that the company had also presented cost-effectiveness analyses comparing reslizumab with omalizumab. The committee recalled its previous conclusion (see section 4.8) that the comparison with omalizumab is highly uncertain and not suitable for decision-making. The committee concluded that it would only consider the company's analysis for reslizumab compared with best standard care using the results from study 3082 and study 3083.

4.10 The committee discussed the choice of standard care in the company's model. The committee was aware that the model did not incorporate stopping or reducing the dose of oral corticosteroids, because oral corticosteroid dose had been kept constant in the trials. It queried whether standard care with long-term maintenance oral corticosteroids is a more appropriate comparator than standard care with oral corticosteroids taken in short courses. The committee recalled the evidence from the clinical experts that 50% of patients with severe eosinophilic asthma may already be on maintenance oral corticosteroids. The clinical and patient experts stated that the long-term effects of oral corticosteroid treatment are serious and could become as problematic as the asthma itself (see

section 4.9). The clinical experts stated some observational data exist on oral corticosteroid sparing and the costs associated with treatment of corticosteroid-induced complications. The committee concluded that because more patients in UK clinical practice have maintenance oral corticosteroids than those in the trials, this is a potential benefit of reslizumab. It concluded that it would be reasonable for the company to explore what impact reslizumab might have on oral corticosteroid usage and its related adverse effects and costs.

Exacerbation transition probabilities

4.11 The committee considered the company's approach to estimating transition probabilities between exacerbation states of the economic model. The company had noted that patients randomised to placebo, as well as those in the reslizumab arm of the trials, experienced a reduction in exacerbations. The company stated that this reflects a potential placebo effect. To account for this placebo effect, the company applied a multiplier to the exacerbation transition probabilities; the value of the multiplier was chosen so that the modelled rate of exacerbations during the first year of treatment matched the mean rate of exacerbations in the year before randomisation to the trial, in those subsequently randomised to placebo. Because the company estimated transition probabilities using data from the subgroup with 2 or more exacerbations in the previous year, the multiplier served a further purpose of adjusting the baseline rate of exacerbations to reflect the subgroup with 3 or more exacerbations, used in the base case. The company adjusted the estimates in both the placebo and the reslizumab arms. The ERG stated that it was unclear why the reslizumab arm should also be corrected for a placebo effect and the company did not provide an adequate explanation. The committee questioned how reasonable it was to make this adjustment (using a multiplier that was estimated with considerable uncertainty), because it could perhaps be accounted for by regression to the mean (that is, the

phenomenon that if patients are recruited into clinical trials when they are experiencing severe symptoms at their first assessment, they will tend to improve on their second assessment regardless of the treatment received). It also heard from the clinical experts that patients in both arms of the trials would be carefully followed and monitored during the trial, so would have had optimised, closely supervised care, which they may not have had before entering the trial. This could account for at least some of the improvement, rather than it being a placebo effect. The committee agreed that improvement could reflect the benefit of optimised care, or regression to the mean. This would be likely to affect both arms, and the adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit of reslizumab. The committee decided that the company should have used estimates of transition probabilities directly from the relevant subgroup of the trials (3 or more exacerbations in the base case), without any adjustment for a placebo effect in either arm of the economic model. The combined adjustment for baseline exacerbation frequency and placebo effect meant that the ERG could not determine the most plausible ICER for the base-case population of 3 or more exacerbations. The committee concluded that it would have preferred to see results from a model that used the observed (unadjusted) data from the relevant subgroup in the trials to determine the transition probabilities. If there are insufficient data to estimate transition probabilities in a particular subgroup then use of a multiplier may be reasonable, but only to adjust for different levels of baseline risk in each subgroup and not to adjust for a possible placebo effect.

Duration of treatment

4.12 The committee discussed the duration of treatment with reslizumab assumed by the company in its model. The committee noted the company's algorithm that calculated the expected response at the end of the year based on an early response at 16 weeks. The clinical experts

stated that patients would not routinely be assessed for response to reslizumab at 16 weeks because this is too early to assess the effect on exacerbations, and other measures would not be reliable enough. A more appropriate reassessment period would be 6 months, followed by annual reassessments. The clinical experts stated that if patients continued to benefit from treatment, they would remain on reslizumab indefinitely. The committee concluded that the economic modelling should include reassessment of patients at time points relevant to UK clinical practice.

Administration costs and drug wastage

4.13 The committee considered the administration costs used by the company in its model. The company assumed that administering reslizumab takes 55 minutes of specialist nurse time (10 minutes for treatment preparation, 30 minutes for treatment administration, and 15 minutes to monitor the patient after treatment administration). The ERG indicated that treatment would initially be done as a day-case admission but monitoring time would decrease as responsiveness and safety were established for the patient. The clinical experts stated that the administration costs might be considerably higher because a day-case admission for intravenous infusion is associated with significant costs, particularly when compared with treatments like omalizumab that are given subcutaneously. The committee concluded that the company should have included more appropriate administration costs for reslizumab in its model.

4.14 The committee noted that reslizumab has a marketing authorisation at a dose of 3 mg/kg given intravenously every 4 weeks, using a 100-mg vial. The committee was aware that the company presented clinical-effectiveness evidence for the licensed 100-mg vial, but that it had applied for a licence extension to include a 25-mg vial. The company had assumed availability of the 25-mg vial in its economic model. The committee was aware that the licence extension is not expected until mid-2017 and it is not guaranteed to receive regulatory approval. The

committee concluded that vial wastage in the economic modelling should be based on the licensed 100-mg vial of reslizumab, including sensitivity analyses around the sharing of vials.

Utility values

4.15 The committee discussed the estimates of utility in the model. It noted that the company's base case used published utility values from Willson et al. (2014) and Lloyd et al. (2007) rather than mapping Asthma Quality of Life Questionnaire (AQLQ) values collected in the trials to EQ-5D. The committee noted the company's justification for using these published values, that they were used in previous NICE appraisals and are direct EQ-5D values. The ERG's view was that the company's base case should have used values mapped from AQLQ to EQ-5D, because the evidence came from the trials. The company presented a scenario analysis incorporating the AQLQ values mapped to EQ-5D. Although the ERG requested full details of the AQLQ and mapped EQ-5D utilities, none were provided by the company. As a result, the ERG could not validate those results. The committee concluded that it would have preferred the company to supply and explain the utility values calculated from the trials.

4.16 The company presented its base case taking into account the patient access scheme discount applied to reslizumab compared with best standard care. The company's base case ICER for people with 3 or more exacerbations in the previous year is £24,907 per quality-adjusted life year (QALY) gained. The committee noted that it was not presented with results for its preferred subpopulation, that is:

- not limited by blood eosinophilia count
- 3 or more, or 4 or more exacerbations in the previous year, and
- limited to patients with severe eosinophilic asthma despite receiving optimised best supportive care at an asthma specialist centre.

The committee considered that the closest population to this was in the ERG's analysis including patients with 2 or more exacerbations in the previous year, which was based on transition probabilities for exacerbations that were not adjusted to the previous year (not adjusted for placebo effect). However, these were also not adjusted to provide the transition probability for the 3 or more exacerbation subgroup, which is the population of interest in the base case. The resulting ICER is £50,878 per QALY gained. The committee was concerned that the 2 estimates, from the company and the ERG, are not related to the same population. Not adjusting for the placebo effect would be likely to increase the company base case ICER above the level that could be considered a cost effective use of NHS resources for people with 3 or more exacerbations. However, the committee concluded that the company should have an opportunity to submit a further cost-effectiveness analysis, taking into account the committee concerns, with no adjustment for placebo effect but including an analysis of the cost effectiveness for people with 3 or more, or 4 or more exacerbations in the previous year, assuming that they are treated in specialist centres with fully optimised care.

4.17 The committee was not satisfied that the cost-effectiveness analysis presented by the company accurately reflected the clinical effectiveness of this treatment in the relevant patient group in the NHS, or the relevant costs. The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include:

- the effect of reslizumab on exacerbations for subgroups of people with 3 or more or with 4 or more exacerbations in the previous year. These should not be adjusted to take account of a placebo effect. Any adjustment related to specific subgroups should be fully explained and justified

- appropriate administration costs including the need to go to hospital for cannula insertion and supervised infusion
- drug wastage using only the licenced100-mg vial
- evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment)
- the individual and combined effects of all amendments on the incremental cost-effectiveness ratios (ICERs) for adults with inadequately controlled severe eosinophilic asthma despite optimised best standard care at specialist centres
- the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.

4.18 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.

4.19 The committee heard from stakeholders that reslizumab is innovative in its potential to make a significant and substantial impact on health-related benefits. The committee heard from the clinical experts that there are few treatments for severe eosinophilic asthma that have the potential to reduce corticosteroid use. It noted that it had not seen any evidence on preventing or delaying maintenance oral corticosteroids but heard from the clinicians that this is an important aim of treatment with reslizumab. 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 calculation. The committee therefore agreed that reslizumab could be considered innovative.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Reslizumab for treating severe eosinophilic asthma inadequately controlled by inhaled corticosteroids**	**Section**
Key conclusion		
The committee is minded not to recommend reslizumab within its marketing authorisation, that is, as an add-on to standard therapy for treating severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal drug product for maintenance treatment in adults. The committee recommends that NICE requests further clarification and an updated cost effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and include: • the effect of reslizumab on exacerbations for subgroups of people with 3 or more or with 4 or more exacerbations in the previous year. These should not include an adjustment for a placebo effect. Any adjustment related to specific subgroups should be fully explained and justified		1.1, 1.2

• appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion • drug wastage using only the licensed 100-mg vial • evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment) • the individual and combined effects of all amendments on the incremental cost-effectiveness ratios (ICERs) for adults with inadequately controlled severe eosinophilic asthma despite optimised best standard care at specialist centres • the committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee understood that people with severe eosinophilic asthma on optimised treatment, described in the high-dose therapies (previously step 4) or continuous and frequent use of oral steroids (previously step 5) stages of the guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network, would be considered eligible for treatment with reslizumab.	4.2

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 concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.	4.7
What is the position of the treatment in the pathway of care for the condition?	The committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.	4.6
Adverse reactions	The most common adverse reaction is increased blood creatine phosphokinase, which is transient and asymptomatic.	Section 2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that there is limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19% and 12% of people respectively in study 3082 and study 3083 fulfilled this criterion. However, the committee concluded that treatment with reslizumab may be considered for people who are not taking	4.6

	maintenance oral corticosteroids but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use.	

Relevance to general clinical practice in the NHS	The committee concluded that the studies are relevant to the UK but that, in clinical practice, patients considered for this treatment may have lower eosinophil counts than in the trials and a higher percentage will be on oral corticosteroids.	4.4
Uncertainties generated by the evidence	The committee noted that study 3082 and study 3083 recruited people with 1 or more exacerbations in the previous year, but the clinical experts stated that they would particularly like to have this treatment available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year. The committee concluded that the results from the company's indirect comparison of reslizumab with omalizumab were highly uncertain and not suitable for decision-making. The committee therefore did not consider this comparison further.	4.5, 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that patients with more exacerbations have a greater clinical need.	4.5

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that, compared with placebo, reslizumab is effective in reducing the rate of clinically significant exacerbations.	4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the company had presented cost-effectiveness analyses comparing reslizumab with omalizumab but that the comparison with omalizumab is highly uncertain and not suitable for decision-making. The committee concluded that it would only consider the company's analysis for reslizumab compared with best standard care using the results from study 3082 and study 3083.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the company's combined adjustment for baseline exacerbation frequency and placebo effect meant that the ERG could not determine the most plausible ICER for the base-case population of 3 or more exacerbations.	4.11

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 noted that the company's base case used published utility values from Willson et al. (2014) and Lloyd et al. (2007) rather than mapping Asthma Quality of Life Questionnaire (AQLQ) values collected in the trials to EQ-5D, and concluded that it would have preferred the company to supply and explain the utility values calculated from the trials. The committee was aware that the model did not incorporate stopping or reducing the dose of oral corticosteroids, because oral corticosteroid dose had been kept constant in the trials. The committee concluded that because more patients in UK clinical practice have maintenance oral corticosteroids than those in the trials, it would be reasonable for the company to consider how reslizumab may affect oral corticosteroid usage and its consequent adverse effects and their costs.	4.15, 4.10

Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted that it was not presented with results for its preferred subpopulation, that is: • not limited by blood eosinophilia count • 3 or more, or 4 or more exacerbations in the previous year, and • limited to patients with severe eosinophilic asthma despite receiving optimised best supportive care at an asthma specialist centre. The committee concluded that it would have preferred to see results from a model which used the observed (unadjusted) data from the relevant subgroup in the trials to determine the transition probabilities.	4.16, 4.11
What are the key drivers of cost effectiveness?	The calculation and choice of exacerbation transition probabilities was the key driver of cost effectiveness for reslizumab compared with best supportive care.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The committee considered that the closest population to its preferred subpopulation was in the ERG's analysis that included patients with 2 or more exacerbations in the previous year, which was based on transition probabilities for exacerbations that were not adjusted to the previous year (not adjusted for placebo effect). The resulting ICER was £50,878 per QALY gained. However, the transition probabilities were also not adjusted to provide the transition probability for the 3 or more exacerbation subgroup, which is the population of interest in the base case.	4.16
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme discount was applied to the ICERs presented by the company and the ERG for reslizumab compared with best standard care.	4.16
End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	No equalities issues were identified.	

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, appraisal committee
October 2016

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz

Technical Lead

Joanna Richardson

Technical Adviser

Liv Gualda

Project Manager