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Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids

Evidence Review Group critique of additional analyses provided by Teva Pharmaceuticals in response to the NICE Appraisal Consultation

Produced by Southampton Health Technology Assessments Centre

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Date completed 19th December 2016

[redacted]

Note: The company's response to the ACD marks CIC data in yellow and AIC data in blue. The ERG has corrected this in the current report so that CIC data are marked in blue and AIC data are marked in yellow, in accordance with the confidentiality checklist provided by the company.

1. Introduction

The first NICE Appraisal Committee Meeting (ACM) for this reslizumab Single Technology Appraisal was held on 18th October 2016. In response to the evidence discussed at the ACM, the NICE Appraisal Committee issued an Appraisal Consultation Document (ACD) recommending that the company (Teva Pharmaceuticals) should provide further information for consideration by NICE at the second ACM.

In this report we provide an independent critique of the additional clinical effectiveness and cost effectiveness evidence and analyses submitted by the company. A summary of the additional information provided by the company is given in Table 1.

As mentioned in the NICE ACD, the British Thoracic Society (BTS)[1] guidelines on asthma were updated in September 2016. The company's ACD Response refers to "BTS GINA step 4" and "BTS GINA step 5". These are equivalent to the steps "High-dose therapies" and "Continuous or frequent use of oral steroids" in the new BTS guidelines.

Table 1. Overview of the additional information provided by the company in comparison to that requested by NICE

Information requested in the ACD	Information provided by the company
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.	Transition probabilities have been updated to be consistent with new unpublished baseline population characteristics and reslizumab efficacy data for [redacted], for subgroups of patients with ≥3 or ≥4 exacerbations in the year preceding enrolment in the pooled pivotal trials 3082 and 3083 (ACD response section 2.1.2). These transition probabilities were amended for the subgroup with ≥4 exacerbations in the previous year by using an exacerbation factor based upon a 'real world' severe asthma cohort to reflect the exacerbation rate observed in clinical practice in this subgroup (ACD Response section 2.1.4).

Appropriate administration costs, including the need to go to hospital for cannula insertion and supervised infusion.	An updated analysis with increased administration costs has been provided (ACD Response section 2.2)
Drug wastage using only the licensed 100 mg vial.	The company has provided the 25 mg vial analysis in the base case and presented the 100 mg vial analysis as a scenario analysis (ACD Response section 2.3).
Evaluation of response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment).	The company has provided the 16-week response analysis in the base case and presented a 6-months response analysis as a scenario analysis (ACD Response section 2.4).
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 company's base case does not incorporate all amendments recommended in the ACD. The ICER of £25,408 is based on the adjustment including 'real world' data. The ICER without this adjustment is £43,064. However, this is for a 25-ml vial size.
The committee recommends that the company also considers how reslizumab may affect oral corticosteroid usage and its consequent	Unpublished information on rescue systemic corticosteroid use was provided from a post hoc analysis in the two pivotal trials 3082 and 3083. However, the company concluded that currently-available data are not robust and did not include steroid sparing in the cost-effectiveness analysis (ACD Response section 2.5).

adverse effects and their costs.	

2. ERG critique of the company's ACD Response

The ERG's critique is provided below, structured to match the order of the sections as they appear in the company's ACD Response. We have also summarised the company's base case (section 3) and we have provided additional analyses to support our preferred base case (section 4).

2.1 Population and transition probabilities

The NICE ACD recommends an updated cost effectiveness analysis on the effect of reslizumab for subgroups of people with ≥3 or with ≥4 exacerbations in the previous year. In order to produce transition probabilities for the ≥3 exacerbations subgroup, the company has presented new data on population characteristics for the subgroup of patients who had ≥3 exacerbations in the previous year and met the criteria for the BTS GINA Steps 4 or 5, using data pooled across the pivotal trials 3082 and 3083 (ACD Response Table 1). The sample sizes of the pooled reslizumab arms and pooled placebo arms are not reported, but the combined sample for both arms comprised [redacted] patients in total. Although using these subgroups breaks the randomisation of the pivotal trials, the population characteristics appear to be similar in the pooled reslizumab and placebo arms.

2.1.2 Efficacy in the target population

The company has presented new 52-week efficacy results pooled from the two pivotal trials for subgroups [redacted] (Table 2 in the ACD Response). These data appear to suggest that reslizumab when compared to placebo resulted in [redacted] in these subgroups. However, the analyses have several limitations: they were post-hoc; they used an unexplained adjustment; the sample sizes for the reslizumab and placebo arms within the exacerbation subgroups are not reported; and the data are confidential so we are unable to verify them.

The company has also presented new 52-week efficacy results, pooled from the two pivotal trials, for subgroups of patients [redacted] (Table 3 in the ACD Response). There are several limitations to these confidential data: it is unclear (not stated) whether the data reported in ACD Response Table 3 are within-group changes in the reslizumab-treated subgroup or changes comparing reslizumab against placebo (sample sizes for patients receiving reslizumab and placebo in the subgroups are not reported); and the analyses are post-hoc.

2.1.3 Transition probabilities

The company has included transition probabilities for patients with ≥3 exacerbations in the previous year as requested by the NICE appraisal committee. The company mentions that the pooled subgroup of patients who had experienced ≥4 exacerbations ([redacted]) was 'insufficient' to estimate transition probabilities in this subgroup. However, no explanation is given as to how this judgement was made. To obtain a transition matrix for the subpopulation with ≥4 exacerbations the company instead made an adjustment based on 'real world' exacerbation rates by changing the exacerbation factor (as explained in ACD Response section 2.1.4).

2.1.4 Rate of exacerbation in the best supportive care arm

The company has provided new 'real world' data on the rate of exacerbations in a severe asthma population. The rationale given by the company is that baseline exacerbation rates in the clinical trials underestimate those in clinical practice (although the NICE appraisal committee had noted that the lower rates of exacerbations in the trials could reflect the effect of optimised asthma care and/or regression to the mean).

The 'real world' exacerbation rate data (shown in Figure 1 in the ACD Response) are taken from [redacted]. As such, we are unable to verify them. The company states that the [redacted]

[redacted]

For comparison with the [redacted] data, the company conducted a 'targeted review' to identify studies documenting exacerbation rates in the population of interest. The methods of the review are not reported. Four additional studies were identified (Table 4 in the ACD Response). Confidential data from a report by Meyers et al. are presented, but the report does not correspond to the Meyers et al. reference provided by the company, which is a conference abstract.[2] The data from Meyers et al. cited in Table 4 of the ACD Response are not given in the conference abstract and so we have been unable to verify them. Further data on the mean number of severe exacerbations (6.24) experienced by patients in a subgroup with ≥4 severe exacerbations are cited as being from a study by Niven et al.;[3] however, these are not reported in the Niven et al. paper referenced by the company and so we cannot verify these either. The study by Niven et al.[3] was in a severe IgE-mediated asthma population, not specifically eosinophilic, whilst other studies identified by the company by Sweeney et al.[4] and Gibeon et al.[5] had median baseline eosinophil counts around 300 per μL.

In summary, there is uncertainty around the 'real world' and published exacerbation rate data which the company has presented (Table 4 of the ACD Response) since no review methods or selection criteria are reported and some of the data cannot be verified.

2.2 Administration costs

The NICE ACD recommends appropriate administration costs, including the need to go to the hospital for cannula insertion and supervised infusion. The company increased the administration costs for the first three visits to account for cannula insertion and increased the initial monitoring time by including costs for a day case admission of £316. For subsequent administrations, the company has increased the nursing time by 10 minutes to 65 minutes to allow for more preparation time. The administration costs used by the company seem reasonable to the ERG although we are not able to comment whether the proposed nursing time is clinically valid.

2.3 25 mg and 100 mg vial presentations

NICE requested that the company should include drug wastage using only the licensed 100 mg vial size. The company has submitted a base case analysis using the 25 mg vial size. The company justifies this by stating that the European Medicine Agency has agreed in principle to support 25 mg vials and these are expected to be available soon after the anticipated date of issue of the final NICE guidance. The company has provided scenario analyses using the 100 mg vial size and also a vial-based dosing scheme using 25 mg and 100 mg vial sizes.

2.4 Evaluation of response

The NICE ACD recommends an updated cost effectiveness analysis that evaluates response to treatment at periods that reflect clinical practice (such as 6 months from the start of treatment). The company has provided arguments for keeping their 16-week response analysis in the updated base case and has included the assessment of response at 6 months as a scenario analysis.

The company has provided new evidence of the early response to reslizumab at 16 weeks (Table 6 in the ACD Response). Limitations are that the analysis was post-hoc, based on subgroups, the sample sizes are not reported, and the data are confidential.

2.5 Oral corticosteroid usage

The company has summarised an analysis of pooled data on the number of 'rescue OCS' prescriptions and the total cumulative dose of corticosteroid from the pivotal trials 3082 and 3083, as reported in a poster by Bardin et al. (which the company cites as Murphy et al.[6]). According to the poster, the prescriptions for systemic corticosteroids [redacted]. The analysis excludes maintenance OCS therapy as this was not permitted to vary during the pivotal trials. Limitations of the analysis are that it was post-hoc, based on subgroups, the sample sizes are not reported, and the data are stated to be confidential (although this appears inappropriate as the poster is referenced to a previous meeting).

The company also mentions an ongoing study of the steroid-sparing effect of reslizumab (NCT02501629) but this is currently recruiting and not due to complete until late 2017 and therefore cannot provide relevant data at present.

The company concluded that there is a lack of robust data on the steroid-sparing effect of reslizumab, and for that reason the effect of reslizumab on OCS use has not been included in their updated economic analysis. Published evidence is available on the oral

corticosteroid-sparing effects in eosinophilic asthma of the closely-related drug mepolizumab (Bel et al.[7]) but the company does not mention this in their ACD response.

2.6 Utilities

The company has amended the utility value for the exacerbation health states using the value suggested in scenario 3 in the ERG report. The utility estimate for the severe exacerbation health state has changed from 0.33 to 0.51. The ERG agrees that this is a more appropriate value to use for the severe exacerbation health state.

2.7 Health state costs

The company has amended the costs associated with each health state on the basis of the ERG suggestions as shown in ACD Table 8. We agree that these values are more appropriate for the health state costs.

3. Summary of the company's base case

The company has provided an updated base case analysis and scenario analyses. The ERG has checked these analyses and has replicated them in the company model submitted.

The company's base case analysis is shown in Table 1. This includes changes from the initially submitted model with the PAS price for resilzumab together with the following changes: updated transition probabilities for patients with ≥3 exacerbations in the previous year, adjustment to the exacerbation rate observed in clinical practice in the UK, updated administration time, updated health state costs, and updated utilities. The company shows the impact of these individual changes in Table 9 of the ACD response. The company's base case assumes the use of 25 mg vials.

Table 1. Company's base case

	Total costs			Total QALYs			ICER
Scenario							
Initially submitted model, Patient Access Scheme (PAS) price							£24,907
Combined effects of all amendments							£25,408

BSC: Best Standard of Care; ICER: Incremental Cost-Effectiveness Ratio; PAS: Patient Access Scheme; QALYs: Quality-Adjusted Life Years

The NICE committee requested that the company's additional analyses should not include an adjustment for a placebo effect and drug wastage should use only the licensed 100 mg vial. The company's base case differs from that requested by NICE in that it includes an adjustment to the exacerbation rate and does not include the analysis with 100 mg vials. The company has included these analyses as scenario analyses (ACD response Table 11 and Table 15). These analyses are shown here in Table 2 and Table 3 for patients with ≥3 and ≥4 exacerbations in the previous year.

Table 2 Company's base case and analyses with no adjustment of exacerbation rate and using 100 mg vials for patients with ≥ 3 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	**Res-lizumab**	**BSC**	**Incre-mental**	**Res-lizumab**	**BSC**	**Incre-mental**	
Base-case: ≥ 3 exacerbations in the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,408
No adjustment to 'real world' rate of exacerbations; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,064
No adjustment to 'real world' rate of exacerbations; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,136

Table 3 Company's base case and analyses with no adjustment of exacerbation rate and using 100 mg vials for patients with ≥ 4 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	**Res-lizumab**	**BSC**	**Incre-mental**	**Res-lizumab**	**BSC**	**Incre-mental**	
Subgroup of patients with ≥ 4 exacerbations in the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,457
Subgroup of patients with ≥ 4 exacerbations in the previous year; no adjustment to 'real	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,715

Scenario	Total costs			Total QALYs			ICER
	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
world' evidence; 25 mg vials							
Subgroup of patients with ≥ 4 exacerbations in the previous year; no adjustment to 'real world' evidence; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,287

4. Additional ERG analyses

The exacerbation rate chosen for the analyses has a large impact on the cost-effectiveness results. The choice of 'real-world' data for the exacerbation rate produces results that are similar to those presented in the original company submission where the company increased the exacerbation rate to a rate similar to that seen in the year before treatment started. As discussed in the NICE appraisal committee meeting, the improvement in exacerbation rate in the clinical trial for placebo patients may be due to better management of patients that led to better medication adherence and hence lower exacerbation rates.

The ERG presents a scenario where the exacerbation rate varies over time. At the start of treatment, patients have an exacerbation rate as seen in the clinical trials (reflecting better initial asthma management), i.e. with no adjustment to the exacerbation rate. Over 10 years the exacerbation rate linearly increases to the exacerbation rate of the 'real world' data. The results for this scenario are shown in Table 4 and Table 5 for patients with ≥3 and ≥4 exacerbations in the previous year.

Table 4 ERG analyses with an increase in the exacerbation rate for patients with ≥ 3 exacerbations in the previous year

Scenario	Total costs			Total QALYs			ICER
	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
Base-case: ≥ 3 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,952
Base-case: ≥ 3 exacerbations in the previous year;	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,471

	Total costs			Total QALYs			ICER
Scenario	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
increasing BSC exacerbation rate; 100 mg vials							

Table 5 ERG analyses with an increase in the exacerbation rate for patients with ≥ 4 exacerbations in the previous year

	Total costs			Total QALYs			ICER
Scenario	Res-lizumab	BSC	Incre-mental	Res-lizumab	BSC	Incre-mental	
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 25 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,439
Base-case: ≥ 4 exacerbations in the previous year; increasing BSC exacerbation rate; 100 mg vials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,754

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