National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Novartis Pharmaceuticals UK	We consider the proposed appraisal appropriate.	Comment noted.
	British Thoracic Society endorsed by the Royal College of Physicians	We welcome the intended consultation on this technology appraisal.	Comment noted.
	Teva Pharmaceuticals	Yes, this topic should be appraised. Asthma with elevated blood eosinophils has emerged as a distinct asthma phenotype. It is associated with the key pathophysiological and clinical features of asthma, including airway remodelling with associated persistent airflow limitation and poor clinical control with risk of asthma exacerbation. There are currently no licensed medicinal products specifically for patients	Comment noted.

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		with asthma and elevated blood eosinophils who are inadequately controlled with inhaled corticosteroids. Reslizumab specifically addresses the clear unmet medical need for an effective, targeted and well-tolerated therapy for this group of patients.	
Wording	Novartis Pharmaceuticals UK	The EMA filing for reslizumab is for the treatment of adult patients and therefore, we believe that the remit should include that this is for adult patients.	Comment noted. Reslizumab will be appraised within the boundaries of its marketing authorisation. The wording of the remit has been amended to "To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids".
	Teva Pharmaceuticals	The currently requested indication is as follows: *'Reslizumab is indicated to reduce exacerbations, relieve symptoms and improve lung function in adult patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.'* The wording of the remit should therefore be amended to: *'To appraise the clinical and cost effectiveness of reslizumab within its*	Comment noted. The wording of the remit has been amended to "To appraise the clinical and cost effectiveness of reslizumab within its

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		marketing authorisation for treating ***adults with asthma and elevated blood eosinophils*** *inadequately controlled by inhaled corticosteroids.'*	marketing authorisation for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids".
Timing Issues	Novartis Pharmaceuticals UK	No comment.	Comment noted.
	Teva Pharmaceuticals	This topic should be appraised as a priority. There is a clear unmet need for treatment options in patients with asthma and elevated blood eosinophils who continue to be substantially impacted by their disease, despite use of current standard of care (BTS/SIGN Asthma Guidelines). More generally, a substantial proportion of patients with asthma remain uncontrolled despite improvements in treatment and the use of guideline-based therapy. This has been attributed to heterogeneity in factors such as the underlying inflammatory pathology. Asthma with elevated blood eosinophils is now recognised as a distinct asthma phenotype, but is one for which no specific therapies have yet been licensed.	Comment noted. NICE aims to schedule technology appraisals into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to issue guidance within 6 months of a technology receiving its marketing authorisation in the UK.
Additional comments on the draft remit	Teva Pharmaceuticals	Yes. We have changed eosinophilic asthma to 'patients with asthma and elevated blood eosinophils' throughout the document. We have done this because eosinophilic asthma is not a disease and we believe it could cause confusion. We believe that asthma with elevated eosinophils provide more clarity around where Reslizumab might be appropriately used and therefore	Comment noted. The scope has been amended accordingly.

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		request that NICE update the terminology wherever it appears in the consultation document including within the title of the draft scope.	

Comment 2: the draft scope

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Background information	Novartis Pharmaceuticals UK	No comment.	Comment noted.
	Teva Pharmaceuticals	The background information provides a useful broad overview and appears to be accurate. In adults, omalizumab is indicated *'as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist*.' However, clinical input suggests that there is a number of patients with difficult or severe asthma are ineligible for omalizumab treatment.	Comment noted. References to omalizumab in the scope are in line with the recommendations for omalizumab in NICE technology appraisal guidance 278.
The technology/ intervention	Novartis Pharmaceuticals UK	It should be noted that the inclusion criteria and the population studied in the reslizumab clinical trials was more restrictive than described. Please comments in the population response for further information.	Comment noted. The population in the scope has been amended to 'Adults with asthma with elevated blood eosinophils

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			inadequately controlled by inhaled corticosteroids'.
	Teva Pharmaceuticals	Teva suggests amending the description to: *'Reslizumab (brand name yet to be determined, Teva Pharmaceuticals) is a humanised anti-human anti-interleukin-5 monoclonal antibody. By reducing the effects of interleukin-5, reslizumab causes a reduction in circulating and sputum eosinophils, a type of white blood cell involved in allergic response and tissue inflammation. Reslizumab is administered by intravenous infusion in addition to best standard asthma care.'*	Comment noted. The technology section of the scope is only intended to provide a brief description of the technology. A detailed description of the technology will be included in the company's evidence submission and will be considered during the appraisal.
Population	Novartis Pharmaceuticals UK	The EMA filing for reslizumab is for adult patients. Therefore, we believe the population should clearly state adult severe eosinophilic asthma. It is currently unclear what the marketing authorisation for reslizumab will be and therefore it is unclear how the licenced population will be defined in terms of blood or sputum eosinophil count, symptom history and medication usage. We believe that the phase III reslizumab population studied should be more clearly reflected in the population: Patients studied in the phase III reslizumab clinical trials had severe asthma rather than more mild of moderate asthma The inclusion criteria in the phase III reslizumab trials regarding eosinophil levels was that patients had to have at least one blood eosinophil count of at 400 cells per µL or higher during the 2 to 4 week screening period. Therefore, we believe that the population should include:	Comment noted. Reslizumab will be appraised within the boundaries of its marketing authorisation. The population in the scope has been amended to 'Adults with asthma with elevated blood eosinophils inadequately controlled by inhaled

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		Adult patients with severe eosinophilic asthma (defined as current blood eosinophil level of at least 400 cells per µL)	corticosteroids'.
	Teva Pharmaceuticals	The population should be: *'**Adults** with **asthma and elevated blood eosinophils inadequately controlled on inhaled corticosteroids'*	Comment noted. The population in the scope has been amended to 'Adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids'.
Comparators	Novartis Pharmaceuticals UK	We agree that best standard care without reslizumab is an appropriate comparator. However, we believe another relevant comparator for the reslizumab population is mepolizumab which is also currently being reviewed by the EMA and for which a technology appraisal is proposed (NICE ID781). Other comparators: We believe that the statement 'For people with severe persistent allergic IgE-mediated eosinophilic asthma should be changed to 'For people with severe persistent allergic IgE-mediated asthma with raised eosinophils'. There is uncertainty regarding the overlap of the severe allergic IgE mediated asthma and severe eosinophilic asthma. For patients with severe persistent allergic Ig-E mediated asthma there may be a proprotion of patients who also have raised eosinophils. However there are no published data on the overlap of severe eosinophilic asthma and severe allergic IgE mediated asthma populations. However, we anticipate that this will be a minority population as suggested by clinicians at the mepolizumab scoping meeting on 13th March 2015.	Comments noted. The comparators in the scope represent established clinical practice in the UK. Therefore, mepolizumab cannot be considered a comparator for reslizumab at this stage. The comparators section in the scope has been amended to specify 'For people with severe persistent allergic IgE-mediated

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		It should also be noted that there are some important differences in the evidence base for reslizumab and omalizumab. There are differences in baseline patient characteristics, study design, study inclusion criteria and defintions of endpoints, including exacerbations. We therefore anticipate that it will be challenging to conduct a robust comparison between reslizumab and omalizumab.	with elevated blood eosinophils'. The Committee will consider the evidence available for the comparison with omalizumab during the appraisal process.
	Teva Pharmaceuticals	Yes, the comparators are appropriate, however it should be noted that on September 24th 2015 mepolizumab received CHMP positive opinion recommending marketing authorisation approval.	Comment noted. The comparators in the scope represent established clinical practice in the UK. Therefore, mepolizumab cannot be considered a comparator for reslizumab at this stage.
Outcomes	Novartis Pharmaceuticals UK	The outcomes listed are appropriate. Additional measures included in the phase III reslizumab trials included: Reduction in blood eosinophils Rescue use of short acting beta antagonists Time to first clinical asthma exacerbation Immunogenicity	Comment noted. The outcomes list in the scope is not prescriptive. Consultees can include additional outcomes in their submission if they considered it to be

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			appropriate.
	Teva Pharmaceuticals	Yes, the listed outcomes are appropriate.	Comment noted.
Economic analysis	Novartis Pharmaceuticals UK	No comment.	Comment noted.
	Teva Pharmaceuticals	A lifetime time horizon will be required to demonstrate any differences on costs or outcomes between the technologies being compared.	Comment noted.
Equality and Diversity	Novartis Pharmaceuticals UK	No comment.	Comment noted.
	Teva Pharmaceuticals	Teva is not aware of any equality issues raised by the proposed appraisal.	Comment noted.
Innovation	Novartis Pharmaceuticals UK	No comment.	Comment noted.
	Teva Pharmaceuticals	Yes. There are currently no licensed medicinal products specifically directed at patients with asthma and elevated blood eosinophils inadequately controlled on inhaled corticosteroids. Reslizumab addresses the unmet medical need for an effective, targeted and well-tolerated therapy for this group of patients.	Comment noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will

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			consider this information during the appraisal process.
Other considerations	Novartis Pharmaceuticals UK	We believe that the statement 'People with severe persistent allergic IgE-mediated eosinophilic asthma' should be changed to 'People with severe persistent allergic IgE-mediated asthma with raised eosinophils'.	Comment noted. The comparators section in the scope has been amended to specify 'For people with severe persistent allergic IgE-mediated asthma with elevated blood eosinophils'.
	British Thoracic Society endorsed by the Royal College of Physicians	We note that it would be important that people started on this treatment are carefully: a. evaluated for diagnosis b. evaluated for compliance (if proposed to start after ICS - then very early and would suggest should be at step 4 without control at least - see BTS/SIGN asthma guideline) c. should be commenced as part of a trials covering asthma units across UK.	Comments noted. The other considerations section in the scope states that best standard care for this population is considered to be step 4 and/or step 5 in the stepwise approach to treatment from the SIGN/BTS guideline (for example, high-dose inhaled corticosteroids and oral corticosteroids). The Committee will

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			consider the management of the condition during the appraisal process.
	Teva Pharmaceuticals	None	Comment noted.
NICE Pathways	Teva Pharmaceuticals	**Where do you consider reslizumab will fit into the existing NICE pathway, Asthma?** Reslizumab will fit into the 'Difficult or severe asthma' part of the NICE pathway, following 'Inhaled corticosteroids' This is equivalent to patients at Step 4/Step 5 in the summary of BTS and SIGN guidelines that is included in the draft scope	Comment noted.
	Novartis Pharmaceuticals UK	What is the overlap between populations with severe allergic asthma and eosinophilic asthma not controlled by inhaled corticosteroids? It is currently unclear what the marketing authorisation for reslizumab will be and therefore it is unclear how the licensed population will be defined in terms of blood or sputum eosinophil count, symptom history and medication usage. Some patients with severe eosinophilic asthma may also have severe persistent allergic IgE mediated asthma and therefore be eligible for treatment with omalizumab. However, there are no published data on the overlap of severe eosinophilic asthma and severe persistent allergic IgE mediated asthma populations. There are also no published data on the proportion of patients with atopy in the phase III reslizumab studies. However, atopy alone does not indicate that these patients would meet the criteria for omalizumab specified in both the marketing authorisation and TA278. There are a number of additional criteria for omalizumab eligibility including medication history, concomitant medication, courses of OCS,	Comment noted. The Committee will consider the evidence available for the comparison with omalizumab during the appraisal process.

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		asthma symptoms, lung function, exacerbation history, baseline IgE level and body weight. The degree of overlap between the population defined as eligible for omalizumab within TA278 and the population anticipated to fall within the reslizumab marketing authorisation is uncertain. It should be noted that NICE TA278 for omalizumab states that patients should be receiving optimised therapy which is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate and therefore omalizumab eligible patients would not be on inhaled corticosteroids alone.	
		Have all relevant comparators been included in the scope? We believe another relevant comparator for the reslizumab population is mepolizumab which is also currently being reviewed by the EMA and for which a technology appraisal is proposed (NICE ID781).	Comment noted. The comparators in the scope represent established clinical practice in the UK. Therefore, mepolizumab cannot be considered a comparator for reslizumab at this stage.
		Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom reslizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? The manufacturer will be best placed to comment.	Comment noted. The characteristics of patients in the subgroups should be clearly defined and

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		However, the published phase III clinical trial results demonstrated that patients with higher baseline exacerbation rate had greater reduction in exacerbation rates with reslizumab treatment. Additionally, results in phase II trials demonstrated that patients with concomitant nasal polyps had greater improvements.	should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanism, special characteristics or other clearly justified factors. The subgroups list in the scope does not preclude the identification of additional subgroups during the appraisal process.
	Teva Pharmaceuticals	**What is the overlap between populations with severe allergic asthma and eosinophilic asthma not controlled by inhaled corticosteroids?** There is overlap between populations with allergic asthma and asthma with elevated blood eosinophils; however, the extent of this has not been clearly defined.	Comment noted. The Committee will consider the evidence available for the comparison with omalizumab during the appraisal process.
		Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom reslizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? The following group should be added to the list of subgroups suggested by	Comment noted. The characteristics of patients in the subgroups should be clearly defined and

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		NICE: • People with late-onset asthma and a blood eosinophil level ≥400 per mm^3.	should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanism, special characteristics or other clearly justified factors. The subgroups list in the scope does not preclude the identification of additional subgroups during the appraisal process.
		Children and young people aged 12 years and older who had eosinophilic asthma not controlled by inhaled corticosteroids were included in the reslizumab clinical trials. Should the use of reslizumab for treating eosinophilic asthma in this population be included in the scope of this appraisal? The reslizumab Paediatric Investigation Plan (PIP) details Teva's strategy to develop this medicinal product in children (6 to <12 years old) and adolescents (12 to <18 years old). The conduct of these clinical trials and subsequent submission for a potential indication are deferred. Therefore, the anticipated indication for reslizumab is in adults. As such (and provided the expected licence is granted), the adolescent group should be removed. However, limited data in the 12 to <18 years old age group is available and	Comment noted. The population in the scope has been amended to 'Adults with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids'.

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		support investigation in this patient population.	
Additional comments on the draft scope	Novartis Pharmaceuticals UK	No comment.	Comment noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Royal College of Nursing
Royal College of Pathologists