Review of TA479; Reslizumab for treating severe eosinophilic asthma

TA479 was published in October 2017 and scheduled to be considered for review in 2020.

Decision

1. TA479 remains relevant and an update is not needed.

Rationale

2. The original guidance was an optimised recommendation. New evidence was reviewed during the review of TA431 – Mepolizumab for treating severe eosinophilic asthma TA671 (section 5). The comparators for reslizumab have changed since the original guidance, from 'best standard care' to benralizumab and mepolizumab (section 4). Reslizumab is recommended for a slightly narrower population that its comparators (see Table 3). Reslizumab and the comparators all have similar clinical effectiveness, but reslizumab is the most expensive of these technologies (see Table 1). In addition, reslizumab requires intravenous delivery so the preferred option is often benralizumab and mepolizumab, which are delivered subcutaneously. Since TA671, there has been no new evidence, therefore the committee is unlikely to recommend reslizumab to a wider population.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

3. No changes have been made to the price of reslizumab since the guidance was published. There is a patient access scheme in place for reslizumab. Teva will continue this without any changes.

As the clinical effectiveness of reslizumab and comparators benralizumab and mepolizumab are similar, a cost comparison can be used to compare the three treatments (see section 5). Please see table 1 for the comparison of costs.

Table 1. Comparison of costs - source: TA671 committee meeting 1 slides (slide 18)

	MPL 100 mg SC			BRL 30 mg SC		RSL 10 mg/ml IV
Formulation	Powder for solution for injection	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Concentration for solution infusion
Drug acquisition cost (list price)						
Cost Year 1	£10,920	£10,920	£10,920	£15,640	£15,640	£14,625
Cost Year 2	£10,920	£10,920	£10,920	£12,708*	£12,708*	£14,625
Administration (administration/preparation/monitoring)						
Admin costs Year 1	£330	£207	£113	£160	£113	£1,064
Admin costs Year 2+	£245	£122	£0	£61	£0	£979
Total costs						
Year 1	£11,250	£11,127	£11,033	£15,800	£15,753	£15,689
Year 2+	£11,165	£11,042	£10,920	£12,769*	£12,708*	£15,604

BRL, benralizumab; IV, intravenous; MPL, mepolizumab; No, number; RSL, reslizumab; SC, subcutaneous; vs, versus
* Dose frequency every 4 weeks Doses 1 to 3 and every 8 weeks thereafter for Year 2+ dose based on average of Year 2 and Year 3, 6.5 for this calculation

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

4. There are no proposed changes to the marketing authorisation that would affect the existing guidance.

The original scope defined comparators as best standard care and omalizumab. The committee considered that the omalizumab and reslizumab would be used for different populations and did not consider omalizumab to be a relevant comparator. The comparators for reslizumab have changed since the original guidance, from 'best standard care' to benralizumab and mepolizumab. Table 2 and 3 summarise the marketing authorisations and NICE recommendations for the three treatments.

Table 2. Marketing authorisations of the technologies - source: TA671 committee meeting 1 slides (slide 3)

	Intervention	Comparators	
	Mepolizumab	**Reslizumab**	**Benralizumab**
Mechanism of action	Monoclonal antibody against anti-interleukin-5 receptor alpha. Reduces eosinophils involved in allergic response and inflammation.		
Marketing authorisation	severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years plus.	adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.	adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus long-acting β-agonists.
Formulation	• Vial (powder) • Pre-filled syringe • Pre-filled pen	• Vial (concentrate)	• Pre-filled syringe • Pre-filled pen
Administration and dose	• 100mg **SC injection** 4 weekly	• **IV infusion** 4 weekly • Dose dependent on patient body weight	• 30 mg **SC injection** 4 weekly for 3 doses, then 8 weekly
ICS: Inhaled corticosteroids; IV: Intravenous; Q4W: every four weeks; Q4W: every eight weeks; SC: Subcutaneous			

Table 3 NICE recommendations for the technologies - source: TA671 committee meeting 1 slides (modified slide 7).

	Mepolizumab (TA671)		Reslizumab (TA479)	Benralizumab (TA565)	
Population	Add-on therapy - as an option for treating severe refractory eosinophilic asthma				
Blood eosinophils	≥300 cells/μL in the previous 12 months and	≥400 cells/μL in the previous 12 months and	≥400 cells/μL in the previous 12 months and	≥300 cells/μL in the previous 12 months and	≥400 cells/μL in the previous 12 months and
Severe asthma exacerbations	≥4 needing corticosteroids in the previous 12 months	≥3 needing corticosteroids in the previous 12 months	≥3 needing corticosteroids in the previous 12 months	≥4 needing corticosteroids in the previous 12 months	≥3 needing corticosteroids in the previous 12 months
Steroid dose requirement	Continuous OCS (at least prednisolone 5mg/day over the previous 6 months	NA	NA	Continuous OCS (at least the equivalent of prednisolone 5mg/day over the previous 6 months	NA
ICS: Inhaled corticosteroids; NA: Not applicable; OCS: Oral corticosteroids; TA: Technology appraisal					

Note: Two double-blind, placebo-controlled, phase 3 studies (NCT02501629 and NCT02452190) comparing 110mg subcutaneous injection of reslizumab with placebo were identified. Fixed-dose subcutaneous reslizumab was not effective in reducing exacerbation frequency in patients with uncontrolled asthma and increased blood eosinophils (≥300 cells/μL), or in reducing the daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe eosinophilic asthma.[1] However, it may suggest the company may try to develop a subcutaneous formulation in the future.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

5. The key uncertainties identified in the original guidance:

    a. There was slight uncertainty in the number of exacerbations to use to define the population.

        i. Experts wanted treatment available for patients having maintenance oral corticosteroids who have 3 or more exacerbations per year.

        ii. The trial was one year long, which is not necessarily indicative of future exacerbation rates as event rates vary from year to year. However, the committee noted a comment that previous exacerbations are a strong predictor of subsequent exacerbations.

    b. There was limited data on the effectiveness of reslizumab for people on maintenance corticosteroids found in the original trials as the dose had been kept constant.

    During the review proposal process, the company did not highlight additional evidence being available.

New evidence identified during RRP searches:

6. Table 4 summarises the nine trials identified in TA671. The searches identified four systematic reviews after January 2018 (the end of searches for TA671),

comparing reslizumab with other asthma treatments such as benralizumab and mepolizumab. No new studies were found in these papers. Findings supported the original guidance, showing a reduction in exacerbation rates[2,3] and the safety and efficacy of reslizumab[4,5] for people with severe eosinophilic asthma.

Table 4: Clinical trials used in the indirect comparisons – source TA671 committee meeting 1 slides (slide 10)

Clinical trials included in the ITC in TA671			
References of trial	MPL	RSL	BRL
MEA115588 [MENSA]	✓		
MUSCA	✓		
NCT00587288		✓	
Study 3081		✓	
Study 3082		✓	
Study 3083		✓	
Study 3084		✓	
SIROCCO			✓
CALIMA			✓

a. The comparators for reslizumab have changed from 'best standard care' in the original guidance, to benralizumab and mepolizumab. Compared to benralizumab and mepolizumab, reslizumab is not recommended for people with ≥ 300 blood eosinophil count and ≥ 4 exacerbations. An indirect comparison was the key clinical evidence in TA671.[6] Clinical effectiveness was considered in number of populations (table 5). No treatment was more clinically effective than

another. However, data was not consistently available for all comparators in the considered populations, especially when both blood eosinophil count and exacerbations were considered. Evidence for all three treatments is only available for populations with 400 or more blood eosinophil count.

Table 5: Analyses feasible in TA671 – source: TA671 committee meeting 1 slides (modified slide 10)

Analyses feasible in TA671							
Blood eosinophil count cells/µL	**≥150**	**≥300**	**≥300**	**≥300**	**≥400**	**≥400**	**≥400**
Exacerbations*	**–*****	**–*****	**≥3**	**≥4**	**–*****	**≥3**	**≥4**
MPL vs BRL	✓	✓	✓	✓	✓	No data**	No data
MPL vs RSL	No data	No data	No data	No data	✓	No data**	✓
RSL vs BRL	No data	No data	No data	No data	✓	No data**	No data

BRL benralizumab; MPL, mepolizumab; RSL reslizumab; rec, recommendation; TA technology appraisal; vs versus

* Exacerbations needing corticosteroids in the previous 12 months; ** Data not consistently available for comparators; *** Not specified

b. New evidence for oral corticosteroid sparing was identified in the searches.[7] A post-hoc analysis of studies 3082 and 3083 looked at the number of corticosteroids prescribed following treatment. Significantly fewer prescriptions were given to those treated with reslizumab than placebo. This provides some evidence towards oral corticosteroid sparing with reslizumab. The evidence of oral corticosteroid sparing across all three treatments remains uncertain.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

7. The relevant guidance NG80 Asthma: diagnosis, monitoring and chronic asthma management was updated February 2020. The review has focused on

increasing inhaled corticosteroid treatment within supported self-management for children and young people. The new recommendations have no implications for this RRP.

Additional comments

8. The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from February 2016 to January 2021 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

Equality issues

9. No equality issues were identified.

Decision paper sign off

Janet Robertson – Associate Director, Technology Appraisals

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids.

Current guidance

1.1 Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:

- the blood eosinophil count has been recorded as 400 cells per microlitre or more
- the person has had 3 or more sever asthma exacerbations needing systemic corticosteroids in the past 12 months and
- the company provides reslizumab with the discount agreed in the patient access scheme

1.2 At 12 months:

- stop reslizumab if the asthma has not re responded adequately or
- continue reslizumab if the asthma has responded adequately and assess response each year.

  An adequate response is defined as:

- a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or
- a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.

1.2 These recommendations are not intended to affect treatment with resluizumab that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without

change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Research recommendations from original guidance

N/A

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be Cross referred into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal remains relevant until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance remains relevant, and an update is not needed	**The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.**	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – Relevant Institute work

Published

Mepolizumab for treating severe eosinophilic asthma. (2021) NICE technology appraisal guidance 671

Benralizumab for treating severe eosinophilic asthma (2019) NICE technology appraisal guidance 565

Reslizumab for treating severe eosinophilic asthma (2017) NICE technology appraisal guidance 479

Mepolizumab for treating severe refractory eosinophilic asthma (2017) NICE technology appraisal guidance 431 (replaced by TA671)

Omalizumab for treating severe persistent allergic asthma (2013) NICE technology appraisal guidance 278

Asthma: diagnosis, monitoring and chronic asthma management (2017, updated 2020) NICE guideline NG80

COVID-19 rapid guideline: severe asthma (2020) NICE technology appraisal guidance NG166

In progress

Dupilumab for treating severe asthma. NICE technology appraisal guidance. Expected publication date: TBC

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

Marketing authorisation: *"add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment".*

List price: £499.99 per 100-mg vial and £124.99 per 25-mg vial (excluding VAT).

Recommendations for reslizumab in TA479 were dependent on the company providing reslizumab with a discount agreed in a patient access scheme. The access scheme takes the form of a simple discount at the point of purchase or invoice.

Proposed marketing authorisation (for this appraisal) and current price

No change.

Registered and unpublished trials

Trial name and registration number	Details
Effect of reslizumab on small airways in asthma RESSAPEA; 2017-003958-16; NL63056.018.17	Randomised, placebo controlled trial on the effects of reslizumab on air trapping and hyperinflation in the lungs at 12 weeks. n = 33 Ongoing 3 year study. First authorised in August 2018

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double-blind, placebo-controlled trials. *The Lancet Respiratory Medicine*. 8 (5): 461-474. Access January 2021.

2. Ramonell, R.P., Iftikhar, I.H (2020). Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations: A Network Meta-analysis. *Lung*. 198: 95–10

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