National Institute for Health and Care Excellence

Health Technology Evaluation

Ravulizumab for treating generalised myasthenia gravis ID4019
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Alexion	Evaluating this topic via the Single Technology Appraisal (STA) route is appropriate and aligns well with the need to provide patients with additional effective options in a timely manner.	Thank you for your comment. No action needed.
	Muscular Dystrophy UK	It is timely and appropriate for this topic to be evaluated by NICE.	Thank you for your comment. No action needed.
Wording	Alexion	Alternative wording proposed below to more accurately reflect the target population for the appraisal. Please see Comment 2 for further details. [redacted]	Thank you for your comment. The remit is intended to broadly reflect the anticipated marketing authorisation as well as the clinical evidence base for ravulizumab, and the referral to NICE from the Department of

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			Health and Social Care for this appraisal. At the scoping workshop, stakeholders indicated ravulizumab could also be offered to patients whose generalised myasthenia gravis is not refractory so a broader remit would be more aligned with this view. Therefore, the words 'refractory' and 'antibody positive' has been removed from the remit.
	Muscular Dystrophy UK	The wording is appropriate.	Thank you for your comment. No action needed.
Timing issues	Alexion	Given the unmet need for additional clinically effective treatments for generalized myasthenia gravis (gMG) in the NHS, the timelines proposed for this STA are considered suitable.	Thank you for your comment. NICE aims to provide guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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	Muscular Dystrophy UK	There is an urgency to this evaluation, to ensure that Ravulizumab can be accessed by patients as close to the date of marketing authorisation as possible.	Thank you for your comment. NICE aims to provide guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
Additional comments on the draft remit	Alexion	As efgartigimod and ravulizumab are expected to be licensed for the same patient population, and their appraisals are likely to run along similar timelines, there should be consistency between the scopes for each appraisal, in terms of the description of the disease, population of interest, comparators, outcomes and subgroups.	Thank you for your comment. Despite substantial similarities between efgartigimod and ravulizumab, stakeholders indicated at the scoping workshop that there are also noticeable differences between the drugs. Therefore, the scopes for each technology are developed to take into account these differences. No further action needed.
	Muscular Dystrophy UK	N/A	Thank you. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alexion	The background sections in both this scope and that for the efgartigimod appraisal (ID 4003) should be consistent, in terms of information provided and referencing. It is important to add (to paragraph one) that myasthenia gravis (MG) that affects only the eye muscles (ocular MG) is distinct from MG that affects muscle groups in the head, neck, trunk, and/or limbs (gMG),[1] which is the population of interest for this submission. In addition to the discussion on the age of patients with MG, it is worth adding that the median age of onset of MG that does not respond to treatment is 36 years of age (interquartile range of 28–51 years).[2] This is important, as it highlights that the symptoms and events of this disorder occur at a young age where patients would otherwise expect to be fit, healthy and productive. In addition to what is presented in this scope, the following points from the efgartigimod scope (ID 4003) should be added: • Paragraph one: 'In around 10% of people these antibodies are not detected.'[3] • Paragraph three: In the ravulizumab draft scope it says that cholinesterase inhibitors are used to treat mild, and some cases of moderate, MG; whereas, in the efgartigimod draft scope it says that anticholinesterases are used to treat mild MG – this should be consistent in both documents • Paragraph three: Thymectomy is mentioned as an option for people with mild disease and antibodies against acetylcholine receptor antibodies (AChR) and people with moderate or severe disease. Further details on the eligibility of patients for thymectomy and its place in the treatment pathway should be added. According to the Association of British	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. The draft scope has been changed to specify the percentage of people in whom antibodies are not detected and make the distinction between ocular and generalised myasthenia gravis.

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		Neurologist's management guidelines for MG, the starting point in the treatment pathway for gMG is to start treatment with pyridostigmine and, for patients who are AChR antibody positive and aged under 45 years, to consider thymectomy[4] • In paragraph three of the efgartigimod scope it additionally notes that 'Eculizumab is also indicated for people whose disease does not respond to treatment and are anti-acetylcholine receptor antibody positive' – as discussed in our responses on comparators, we do not believe that eculizumab is a relevant comparator; however, if mentioned, it is important to note that it is not recommended or used in England or Wales References 1. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000; 55(1):16-23. 2. Suh J, Goldstein JM and Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. Yale J Biol Med. 2013; 86(2):255-60. 3. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain. 2008; 131(Pt 7):1940-52. 4. Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol. 2015; 15(3):199-206.	
	Muscular Dystrophy UK	This is accurate.	Thank you for your comment. No action needed.

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Population	Alexion	[redacted]	Thank you for your comment. The population in the scope is kept broad. If the marketing authorisation is narrower, the appraisal committee will consider that population in the appraisal. No action needed.
	Muscular Dystrophy UK	Yes [the population is defined appropriately].	Thank you for your comment. No action needed.
Subgroups	Alexion	At this time Alexion do not expect there to be any specific subpopulations narrower than the target population described above in whom ravulizumab may provide greater clinical benefits or more value for money. Further, gMG is a rare condition and any subsequent assessment of patient subgroups should be made in consideration of the relative size of those subpopulations and the availability of data specifically in those groups.	Thank you for your comment. All subgroups have been removed following the scoping workshop discussion.
	Muscular Dystrophy UK	The population are defined appropriately. We do not feel that any groups should be considered separately.	Thank you for your comment. All subgroups have been removed following the scoping workshop discussion.
Comparators	Alexion	The relevant comparator to ravulizumab in this indication is established clinical management, as defined in the efgartigimod draft scope, including corticosteroids and immunosuppressive therapies, with or without intravenous	Thank you for your comment. Following the stakeholder discussions

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		immunoglobulin or plasma exchange. Eculizumab has not been recommended by NICE for use in NHS England and is not being used by any patients in England or Wales. Eculizumab therefore should not be considered a relevant comparator. [redacted] Rituximab does not have a marketing authorization in the UK for this indication. Although it is used off-label for patients with gMG, its placement in the clinical pathway is later than the proposed positioning of ravulizumab. The NHS England Commissioning Policy recommends that rituximab can be considered for MG patients, who demonstrate active disease despite treatment with maximal immunosuppression: this includes maximal dose of corticosteroids and at least two trials of a steroid-sparing immunosuppressant (for example azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus) for an adequate period of time, in an adequate dose; whereas ravulizumab is licensed for use following only one trial of an immunosuppressant i.e. the preceding line of therapy.[5] There is also limited evidence demonstrating the efficacy of rituximab in patients with anti-AChR antibody positive gMG. Recent clinical evidence suggests that rituximab is not effective in these patients[6]. This is supported by the opinion of clinical experts who also note that treatment with rituximab is associated with slow onset of efficacy, with some patients only achieving a response 6-12 months following treatment initiation. Clinical experts also confirmed that the majority of current rituximab use is in Muscle-Specific Kinase (MuSK) antibody positive rather than AChR antibody positive patients. Therefore, rituximab should not be considered a relevant comparator for ravulizumab in this indication. Intravenous immunoglobulin and plasma exchange are mostly used to treat	at the scoping workshop, the draft scope has been changed to 'Established clinical management without ravulizumab including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin or plasma exchange'.

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		crises, and not for chronic treatment of MG. Therefore, these would be considered a background therapy, rather than a relevant comparator in their own right. This is how they have been included in the efgartigimod draft scope and they should be used consistently across both scoping documents. Thymectomy would also not be considered a relevant comparator for this appraisal. According to the Association of British Neurologist's management guidelines for MG, the starting point in the treatment pathway for gMG is to start treatment with pyridostigmine and, for patients who are AChR antibody positive and aged under 45 years, to consider thymectomy.[4] Therefore, thymectomy would be expected to be used as first-line therapy for those patients that are willing and able to receive it, and would not be a relevant comparator to ravulizumab in this indication. Best supportive care, as currently included in the draft scope (including deep venous thrombosis prophylaxis; ulcer prophylaxis; adequate nutrition and hydration; and avoidance of infections and drugs that may worsen myasthenia symptoms) appears to be normal background care for patients and not specific treatments for MG; therefore, it is not appropriate to consider these as a relevant comparator in their own right.	
	Muscular Dystrophy UK	It is important to consider whether this treatment should be used in addition to the current standards of care rather than a replacement. It would provide additional clarity to reiterate this within the scope.	Thank you for your comment. The technology description in the draft scope is intended to broadly reflect the anticipated marketing authorisation as well as the clinical evidence base for ravulizumab. The appraisal committee will

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			consider the dosing regimen and whether ravulizumab will be in addition to standard care or alone, in line with the marketing authorisation, during the appraisal. No action needed.
Outcomes	Alexion	Change in Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score is missing from the current scope; this was the primary outcome of the pivotal ravulizumab clinical study (the CHAMPION study) and is an important measure of the impact of gMG on patients. This outcome has also been included in the draft scope for efgartigimod (ID 4003) and should be included here for consistency.	Thank you for your comment. At the scoping workshop, stakeholders indicated that 'time to response to treatment' and 'time to clinically meaningful improvement' are important outcomes for clinicians and patients. Therefore, 'improvement in myasthenia gravis' has been added as an outcome in the scope and is considered to include Change in Myasthenia Gravis-Activities of Daily Living score. Please note that outcomes are defined

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			broadly at the scoping stage. Specific outcomes can be defined in the submission and will be assessed by the appraisal committee during the appraisal.
	Muscular Dystrophy UK	Yes, ensuring that the mental health aspects within the health-related quality of life (for patients and carers) outcomes are explicitly reviewed.	Thank you for your comment. No action needed.
Equality	Alexion	NA	Thank you. No action needed.
	Muscular Dystrophy UK	It is important to ensure that no patient has to travel excessive distances to receive the treatment given the level of disability that many will face.	Thank you for your comment. At the scoping workshop, stakeholders indicated that this is not an equality consideration, but it is an issue that affects patients often across all the conditions covered by Muscular Dystrophy UK and should be taken into consideration. Where relevant and appropriate, the

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			appraisal committee will consider the impact of its recommendations on protected characteristics as stated in equality legislation during the appraisal. No action needed.
Other considerations	Alexion	As ravulizumab and efgartigimod (ID 4003) are expected to be licensed for the same patient population, there should be consistency between the scopes for each appraisal. In response to the comment 'The availability and cost of biosimilar and generic products should be taken into account', per the NICE manual (Section 4.4) we will use the relevant prices at time of submission. If data are not available via publicly accessible sources, we will note this for the EAG.	Thank you for your comment. Despite substantial similarities between efgartigimod and ravulizumab, stakeholders indicated at the scoping workshop that there are also noticeable differences between the drugs. Therefore, the scopes for each technology are developed to take into account these differences. No action needed.
	Muscular Dystrophy UK	We recommend that the following questions are also addressed: Do you consider that the use of Ravulizumab can result in any potential	Thank you for your comment. Where appropriate, information about health-related

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		significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Do you consider that there will be any barriers to adoption of this technology into practice?	benefits that are unlikely to be included in the QALY calculation and barriers to adoption of ravulizumab into clinical practice will be included in the submission and assessed by the appraisal committee during the appraisal.
Questions for consultation	Alexion	**Is the Myasthenia Gravis Foundation of America (MGFA) classification system used in the NHS?** Yes the MGFA classification is used in current clinical practice **Would ravulizumab be used in people with myasthenic crisis (MGFA class 5)?** Use of ravulizumab for myasthenic crisis is not included within the proposed license, and therefore ravulizumab would not be used for these patients. **How is refractory generalized myasthenia gravis determined or defined clinically?** The International consensus guidelines define refractory gMG as being unchanged or worse after corticosteroids and at least two other immunosuppressant agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician.[7]	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

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		Have all relevant comparators for ravulizumab been included in the scope? The relevant comparator to ravulizumab in this indication is established clinical management, as defined in the efgartimod draft scope, including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin or plasma exchange. The other treatments included in the draft scope should not be considered relevant comparators for this indication, for the reasons outlined in the relevant section above.	Thank you for your comment. The list of comparators has been amended in line with comments from consultation and the stakeholder discussion at the scoping workshop. No further action needed.
		Are the outcomes listed appropriate? As discussed above, Change in Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score is missing from the current scope; this was the primary outcome of the pivotal ravulizumab clinical study (the CHAMPION study) and is an important measure of the impact of gMG on patients.	Thank you for your comment. Change in Myasthenia Gravis-Activities of Daily Living Score is considered to be covered by the newly added outcome 'improvement in myasthenia gravis'. No further action needed.
		Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom ravulizumab is expected to be more clinically effective and cost effective or other groups that	Thank you for your comment. All subgroups have been removed

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		should be examined separately? At this time Alexion do not expect there to be any specific subpopulations narrower than the target population described above in whom ravulizumab may provide greater clinical benefits or more value for money. Further, gMG is a rare condition and any subsequent assessment of patient subgroups should be made in consideration of the relative size of those subpopulations and the availability of data specifically in those groups. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** Alexion does not believe the proposed remit and scope could exclude any people protected by the equality legislation who fall within the patient population eligible for ravulizumab. Alexion does not believe the proposed remit and scope could have any adverse impact on people with a particular disability or disabilities. Alexion does not believe the proposed remit and scope could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population. **Do you consider ravulizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** gMG is a chronic condition that requires long-term management with appropriate interventions. For patients with gMG still experiencing symptoms	from the scope. No further action needed. Thank you for your comment. No further action needed. Thank you for your comment. No further action needed.

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		despite immunosuppressive treatment and who are in need of an optimal treatment that achieves consistent symptom control, ravulizumab is an innovative solution that provides continuous disease control in an area of severe unmet need. Ravulizumab enables a broad spectrum of gMG patients to regain and maintain control of their lives with the best-in-class C5 inhibitor, a population who otherwise would continue to experience persistant poor outcomes on current care. **Do you consider that the use of ravulizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Through presentation of a cost-effectiveness analyses Alexion will include all relevant benefits that can be expressed within the QALY calculations whilst being adherent to the NICE reference case. Considering the orphan nature of the condition it may be that additional benefits are unable to be captured due to a scarcity of data and this should be bared in mind during the appraisal. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Alexion does not envisage there will be any barriers to adoption of ravulizumab into practice. Ravulizumab is likely to be prescribed and administered to patients via the existing routes already in place for treating patients with gMG within the NHS. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the**	Thank you for your comment. No further action needed. Thank you for your comment. No further action needed. Thank you for your comment. No further

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		appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). As discussed above, evaluating this topic via the Single Technology Appraisal (STA) route is appropriate.	action needed.
	Muscular Dystrophy UK	Nothing to add.	Thank you. No action needed.
Additional comments on the draft scope	Alexion	N/A	Thank you. No action needed.
	Muscular Dystrophy UK	Nothing to add.	Thank you. No action needed.

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

CSL Behring UK
Genetic Alliance UK