National Institute for Health and Care Excellence

Health Technology Evaluation

Ravulizumab for treating AQP4 antibody-positive neuromyelitis optica spectrum disorder [ID5105]

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	Walton Centre	Appropriate. There is unmet need for new treatments in NMOSD in the UK. Only off-label drugs with a significant failure rate are currently available as 1st line treatment.	Comment noted, no action required.
	Oxford University Hospitals NMO service	Re algorithm: 3rd line option Cyclophosphamide is thought to worsen aqp4 disease and the licensed therapies are unavailable in the UK expect for IVIG which is not highly efficacious and is very expensive and in short supply	Comment noted, no action required.
	Alexion	Alexion accepts that HTA of ravulizumab in NMOSD is appropriate, however, we do not consider it appropriate that this technology is routed to the single technology appraisal (STA) process. NMOSD is an ultra rare disease, affecting fewer than 1 in 50,000 people in the UK and as such, we believe the technology should be assessed via the Highly Specialised Technology (HST) programme.	Comment noted. Following the consultation it was decided that this topic will proceed as a Single Technology Appraisal.

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		The NICE health technology evaluation topic selection manual indicates that the HST programme "evaluates technologies for very rare, and often very severe diseases that need specific considerations and flexibilities, for very small numbers of patients with limited or no treatment options and with challenges for research and difficulties with collecting evidence because of the uniqueness of the disease". Alexion maintains that ravulizumab in NMOSD satisfies these needs. Further, we believe ravulizumab in NMOSD satisfies all 4 HST routing criteria: **1. Condition is very rare** NMOSD is a very rare disease with diagnosed prevalence rates of <1 per 50,000 people. **2. No more than 300 people on treatment in the indication and no more than 500 people on treatment across all indications** In NMOSD, it is anticipated that ravulizumab use in UK clinical practice would be [redacted] with an estimated [redacted] patients likely to receive treatment. Ravulizumab is currently used in the NHS for the treatment of two other ultra-rare indications PNH [redacted]) and aHUS ([redacted]). In addition, ravulizumab recently received authorisation for a license extension to include treatment of AChR-antibody-positive gMG adult patients where an estimated [redacted] patients could receive treatment based on [redacted]. **3. Target disease significantly shortens life or severely impairs QoL** NMOSD is a severely disabling disease that is characterised by relapses that can cause blindness, paralysis, and increased overall mortality. Almost all patients experience relapses, and patients find it difficult to live with NMOSD because relapses are unpredictable and vary in their timing, duration, and impact.	This decision was informed by the highly specialised technologies routing criteria, specifically criteria 2 (the population size). As outlined in NICE's Process and Methods manual, "standard technology appraisals methods and processes are designed to be flexible and adaptable for all technologies and conditions. So, they are suitable for most technologies that treat rare conditions and small populations."

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		The symptoms and relapses of NMOSD ultimately translate into disease progression and mortality. Prognosis is generally poor because most patients do not recover fully after each relapse, and neurologic impairment accumulates, resulting in severe disability. Deaths from NMOSD are mostly due to respiratory failure after cervical myelitis attacks, multi-organ failure, or as a result of long-term quadriplegia. The unpredictable nature of NMOSD relapses and the severity of symptoms have marked impacts on activities of daily living, social relationships, and emotional health. Quality of life is substantially affected due to loss of vision, especially when both eyes are affected. Other frequently reported NMOSD symptoms such as fatigue, pain, bladder and bowel problems are not just physically burdensome, but also negatively impact quality of life and interfere in many aspects of life. Disease associated Pain also has a substantial impact on quality of life. NMOSD also affects mental components of health related quality of life with patients experiencing anxiety and depression. 4. No other satisfactory treatment options/ treatment offers significant additional benefit over existing options There is currently no cure for NMOSD and as such, the main goal of treatment is to reduce relapse risk and frequency to minimise the development of long-term disability. Immunomodulatory and immunosuppressive therapies are currently used to manage NMOSD. However, patients treated with these current treatment options still experience relapses and treatment-related side effects limit their use. Consequently, significant unmet need remains for more effective treatment options in NMOSD. Evidence from clinical trials indicated that ravulizumab had a significant positive effect on relapse risk: *(Vu, T; Meisel A et al; Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evid 2022: 1 (5). DOI: https://doi.org/10.1056/EVIDoa2100066)*	

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		• Ravulizumab was able to reduce the risk of relapse by 98.6% compared with placebo (Hazard ratio: 0.014) • At 48 weeks, the proportion of patients who remain relapse free at 48 weeks was 100% for ravulizumab 63.2% for placebo (p<0.0001) • No patients had an adjudicated relapse in the ravulizumab group while on treatment (81.42 patient years of follow-up), compared with 20 of 47 patients in the placebo group (46.93 patient years); (p<0.0001) In addition to the above, we should also like to draw to NICE's attention the fact that the current NMOSD services for managing patients within the NHS are commissioned through highly specialised commissioning services. Given that NMOSD is considered by the NHS to require highly specialised services for management, and ravulizumab in NMOSD satisfies the highly specialised technology appraisal criteria as detailed above, Alexion requests that NICE reconsiders its routing decision to STA in favour of HST.	
Wording	Walton Centre	Yes, no additional comments	Comment noted, no action required.
	Oxford University Hospitals NMO service	The wording does not identify the high risk of death and risk of wheelchair bound with relapse and only focusses on visual impairment	Comment noted. The background section has been updated to address this.
	Alexion	Yes	Comment noted, no action required.
Timing	Walton Centre	We consider the lack of availability to licensed drugs for NMOSD to be an urgent issue of significant importance.	Comment noted, no action required.

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	Oxford University Hospitals NMO service	Very urgent, 50% relapse on 1st line treatment in 2 yrs (Palace et al, Brain 2019;142:1310-23), 48% on ritux as 2nd/3rd line (Mult Sclerosis 2016 Jun;22(7):955-9) (see algorithm) so many patients are in trouble from disabling relapses currently	Comment noted, no action required.
	Alexion	NMOSD is a debilitating disease associated with relapses that lead to cumulative disability and is associated with high mortality and morbidity. At present, there is no cure for NMOSD and there are no licensed treatment options for the disease available to patients within the UK NHS. Current treatment options are general immunosuppressive therapies and many patients continue to experience symptoms and relapses despite treatment. Ravulizumab is a novel treatment option that has the potential to substantially reduce the risk of relapse and thus reduce the accumulation of disability, and thereby alter the course of disease. It is therefore imperative that NICE completes the appraisal of ravulizumab in NMOSD in a timely manner to allow patients the opportunity to access this innovative therapy.	Comment noted. NICE aims to publish final guidance for all new technologies within 90 days of receiving marketing authorisation.
Additional comments	Oxford University Hospitals NMO service	AQP4 from UK prevalence study should have 672 patients in england O'Connell K, et al JNNP doi: 10.1136/jnnp-2020-323158	Comment noted. This data has been added to the background section.
	Alexion	A publication by Royston, Kielhorn et al in Neurol Ther in 2021 has been published indicating that NMOSD therapies with the highest relapse risk reduction could lead to markedly lower relapse-associated healthcare utilization and clinical burden in patients with NMOSD. *(Royston, M., Kielhorn,*	Comment noted. The company is invited to include this information within its evidence

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		A., Weycker, D. et al. Neuromyelitis Optica Spectrum Disorder: Clinical Burden and Cost of Relapses and Disease-Related Care in US Clinical Practice. Neurol Ther 10, 767–783 (2021). https://doi.org/10.1007/s40120-021-00253-4)	submission. The clinical and cost-effectiveness of the technology will then be considered by the committee during the appraisal.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Walton Centre	The wording in background section should clearly state that available 1st line treatments for NMOSD have not been tested in randomised clinical trials. Brain involvement should be mentioned in the clinical features of the disease. Even with effective treatment of relapses, severe disability is not uncommon.	Comment noted. The background section aims to provide a general overview of the topic and as such, would not include details about the availability of clinical evidence. The section has been updated to specify that relapses and disability occur despite current treatment. It also now mentions brain involvement.

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	Oxford University Hospitals NMO service	AQP4 from UK prevalence study should have 672 patients in england O'Connell K, et al JNNP doi: 10.1136/jnnp-2020-323158	Comment noted. This data has been added to the background section.
	Alexion	The background information as presented in the draft scope is accurate. Alexion would like to point out that while the information on APQ4 antibody-positive NMOSD patient numbers in the background information is reflective of the literature, based on discussions with UK clinical experts, it is our understanding that ravulizumab use in NMOSD [redacted] (as per the treatment algorithm provided), with an estimated [redacted] patients likely to receive treatment in England. [redacted]	Comment noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal.
Population	Walton Centre	Yes	Comment noted, no action required.
	Oxford University Hospitals NMO service	Yes	Comment noted, no action required.
	Alexion	We anticipate ravulizumab will be licensed [redacted]	Comment noted, no action required.

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Subgroups	Walton Centre	No additional comments	Comment noted, no action required.
	Oxford University Hospitals NMO service	I would focus on patients failed ritux as this is main unmet need extrapolating from the eculizumab data as this showed efficacy and safety in a larger study and this study extended the data using a longer acting more practical formulation	Comment noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal.
	Alexion	At this time, Alexion does not expect there to be any specific sub-populations in whom ravulizumab may provide greater clinical benefits or value for money. Further, as NMOSD is an ultra-rare condition, any assessment of patient subgroups should consider the relative size of those subpopulations and the availability of data specifically in those groups.	Comment noted, no action required.
Comparators	Walton Centre	No additional comments	Comment noted, no action required.
	Oxford University Hospitals NMO service	Yes except we don't use cyclophosphamise as case series suggest harmful and the lisenced drugs unavailable	Comment noted, no action required.
	Alexion	Clear definition is required of the products considered to be established clinical management without ravulizumab.	Comment noted. 'Established clinical management without the technology' is a standard phrase used in

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			scopes and is not normally defined. The committee will determine what is clinical management without ravulizumab during the evaluation.
Outcomes	Walton Centre	Expanded disability status scale should be included.	Specific measurement scales are not typically included in this section.
	Oxford University Hospitals NMO service	There is a very high morbidity and mortality Kitley, *et al. Brain* 2012 *doi:10.1093/brain/aws109* and thus time to one relapse is the only safe outcome and disability is soley related to relapse as there is no progressive phase. This does not come over in the background either. Thus the relative risk on time to relapse will need to be modelled to estimate the effect on disability including edss and death even to obtain cost per qaly .	Comment noted, no action required. Stakeholders will be invited to submit evidence and statements during the appraisal which will be considered by the committee.
	Alexion	The outcome measures included in the draft scope are broadly aligned with the outcomes captured from clinical trials with the exception of bowel and bladder continence which was not captured. As no data on this endpoint will be available, we suggest this outcome should not remain within the scope of the appraisal. While not measured directly, as bowel and bladder continence are expected to impact patient HRQoL, they will be captured through EQ-5D and other patient reported outcome tools.	Comment noted, no action required. The company is invited to include this information within its evidence submission. All evidence and statements will be

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		It should also be noted that visual acuity was included in the clinical trial only as an exploratory endpoint and no comparative efficacy will be available on this endpoint as it was not captured in the study which provides the external placebo control data.	considered by the committee.
Equality	Walton Centre	No additional comments	Comment noted, no action required.
	Oxford University Hospitals NMO service	This disease affects black and Asian people more than white people	Comment noted. The background section has been updated to include the disproportionate impact of the condition on people of black and Asian ethnicity. Issues related to differences in prevalence of a disease cannot typically be addressed in a technology appraisal. However, the committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

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	Alexion	While we have not identified any equality issues within the draft scope, as NMOSD disproportionately impacts women as well as Black and Asian people, this should be borne in mind when conducting this appraisal given gender and ethnicity are protected characteristics.	Comment noted. The background section has been updated to include the disproportionate impact of the condition on people of black and Asian ethnicity. Issues related to differences in prevalence of a disease cannot typically be addressed in a technology appraisal. However, the committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
Other considerations	Walton Centre	Disability in NMOSD is relapse driven. If early high efficacy treatment is readily available this will have significant impact on reducing final disability, preserving independence and the ability to work/contribute in community	Comment noted, no action required.
	Alexion	None	Comment noted, no action required.

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Questions for consultation	Walton Centre	*Does the NMO UK Treatment Algorithm reflect established clinical management for NMOSD in England? How would established clinical management without ravulizumab be defined?* No, third line therapies in the algorithm are not currently available- Eculizumab, Satralizumab, and Inebilizumab. *Where do you consider ravulizumab will fit into the existing care pathway for NMOSD? Would it only be used to prevent relapse?* 3rd line treatment for relapse prevention in patients that relapse despite Rituximab. Depending on cost, 1st line treatment could also be considered. *How many patients are likely to be eligible for treatment in England? Would all people with aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (NMOSD) be eligible?* If considered for 3rd line treatment this would be applicable to less than 10% of aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (NMOSD) patients.	Comments noted, no action required.
	Alexion	**Q: Does the NMO UK Treatment Algorithm reflect established clinical management for NMOSD in England? How would established clinical management without ravulizumab be defined?**	Comments noted, no action required.

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		A: The NMO UK Treatment Algorithm broadly reflects the care pathway in the whereby intravenous steroids and plasma exchange have formed the standard approach to treating acute attacks to stabilise patients. Once stabilised, various types of immunosuppressive therapy have been used to try to prevent further attacks and, most importantly, avoid the significant morbidity that is associated with acute attacks. We note that the treatment algorithm includes 3 treatments as 3rd line options (satralizumab, inebilizumab and eculizumab) that are either not yet licensed in the UK or not available for use in clinical practice in the NHS. We therefore do not consider that these treatments should be included in the algorithm or considered to be within the scope of this appraisal. **Q: Where do you consider ravulizumab will fit into the existing care pathway for NMOSD? Would it only be used to prevent relapse?** A: The anticipated licensed indication for ravulizumab [redacted] Data from clinical trials showed ravulizumab reduced the risk of relapse by 98.6% compared with placebo (HR 0.014) and 100% of patients treated with ravulizumab remained relapse free at 48 weeks of follow-up. **Q: How many patients are likely to be eligible for treatment in England? Would all people with aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (NMOSD) be eligible?** A: NMOSD is an ultra rare disease with diagnosed prevalence estimated at ~1.5 per 100,000 population. Between 70-80% of NMOSD patients will have	

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		anti-AQP4 antibodies. [redacted]. **Q: Would ravulizumab be a candidate for managed access?** A: In the interests of making our medicines available to UK patients, in the event that NICE is unable to make a recommendation for routine commissioning without additional data collection to address clinical uncertainties, Alexion may be prepared to consider a managed access arrangement. **Q: Do you consider that the use of ravulizumab can result in any potential 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 committee to take account of these benefits.** A: 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 borne in mind during the appraisal.	
Additional comments on the draft scope	Walton Centre	n/a	Comments noted, no action required.