National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating atypical haemolytic uraemic syndrome (aHUS) ID1530

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Alexion Pharmaceuticals UK	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted. No action required.
	aHUS alliance Global Action	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted. No action required.
	British Association for Paediatric Nephrology	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Comment noted. No action required.
	Kidney Research UK	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	Comment noted. No action required.

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		Yes	
	NHS England and Improvement	Yes, the remit does address the clinical issues and the cost effectiveness	Comment noted. No action required.
Timing Issues	Alexion Pharmaceuticals UK	A timely evaluation by NICE is required to provide guidance to NHS England as soon as possible to inform national commissioning decisions given EMA marketing authorisation for ravulizumab in aHUS was granted in June 2020.	Thank you for your comment. NICE has scheduled this topic into its work programme. For further information please see the project information page for this appraisal.
	aHUS alliance Global Action	Urgent to improve lives and save money	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed. For further information please see the project information page for this appraisal.
	British Association for Paediatric Nephrology	There is currently an effective treatment for atypical HUS commissioned by NHS England and available for patients in England - eculizumab. The main impact of Ravulizumab is likely to be an improved quality of life for patients because of reduced frequency of infusions and a reduced burden on NHS resources due to a reduction in treatment visits. There is limited urgency unless ravulizumab offers a significant cost-saving over eculizumab.	Comment noted. No action required.

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	Kidney Research UK	There is currently an effective treatment for atypical HUS commissioned by NHS England and available for patients in England (Eculizumab). Eculizumab and Ravulizumab share the same mechanism of action, the main difference being the frequency of dosing (2 weeks vs 8 weeks respectively) for maintenance treatment for most patients. The approval of Ravulizumab would represent a benefit in management of patients aHUS but for a relatively small proportion of patients. Therefore, there is limited clinical urgency. There may be financial considerations if the cost of Ravulizumab is significantly lower than the cost of Eculizumab.	Comment noted. The clinical- and cost-effectiveness of ravulizumab relative to eculizumab will be appraised using the framework as set out in the NICE Guide to the methods of technology appraisal. No action required.
	NHS England and Improvement	Other treatment options are available for this patient group, we would therefore not consider there to be a need to urgently prioritise this work	Comment noted. No action required.
Additional comments on the draft remit	Alexion Pharmaceuticals UK	None	Comment noted. No action required.
	British Association for Paediatric Nephrology	NO	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background	Alexion	The draft scope states that aHUS is associated with an underlying genetic or	Thank you for your

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information	Pharmaceuticals UK	acquired abnormality of proteins in the complement system in approximately 70% of patients; we believe this is at the high end of the values presented in the literature, which range from 45-70% and the text should therefore be amended accordingly.	comment. The background section of the scope has been updated to reflect this.
	aHUS alliance Global Action	Sufficiently accurate and complete	Comment noted. No action required.
	British Association for Paediatric Nephrology	aHUS does not cause inflammation in blood vessels, it causes blood clots in the small blood vessels in the kidney and other organs. Otherwise accurate	Thank you for your comment. The background section of the scope has been updated to reflect this.
	Kidney Research UK	It is stated that aHUS is characterised by severe inflammation in blood vessels. There may be some inflammation but aHUS is not a disease characterised by a major inflammatory component. Vessel occlusion by microthrombi and vascular wall injury are more characteristic features.	Thank you for your comment. The background section of the scope has been updated to reflect this.
	NHS England and Improvement	The clinical team in Newcastle has recently completed a data reconciliation and the number of patients on the SETs trial has increased the number of patients receiving treatment is now nearer the lower end of the range provided. Other than this the background is adequate.	Comment noted. No action required.
The technology/ intervention	Alexion Pharmaceuticals UK	The technology/intervention section should be updated to reflect that on June 25 2020, the EMA granted marketing authorisation on for ravulizumab for the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have	Thank you for your comment. The technology section of the scope has been

Section	Consultee/ Commentator	Comments [sic]	Action
		evidence of response to eculizumab.	updated to reflect this.
	aHUS alliance Global Action	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	British Association for Paediatric Nephrology	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	Kidney Research UK	*Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	NHS England and Improvement	The description of the technology is accurate.	Comment noted. No action required.
Population	Alexion Pharmaceuticals UK	The population description could be changed to align with the licensed indication as follows: People who weigh 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.	Comment noted. Written in NICE style, the population section of the scope aligns to the wording of the marketing authorisation. No action required.
	aHUS alliance Global Action	*Is the population defined appropriately? Are there groups within this population that should be considered separately?* Yes. No.	Comment noted. No action required.
	British Association for	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Comment noted. No

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	Paediatric Nephrology	Yes.	action required.
	Kidney Research UK	The draft scope accurately defines the population who could receive Ravulizumab. There are a proportion of patients who require long-term treatment and therefore will gain significant benefit from the reduction in dosing frequency possible with Ravulizumab. Consideration of this group in terms of patient number would inform the likely impact of the outcome of this appraisal. Patient feedback from patients who may be eligible for Ravulizumab treatment highlights the potential benefits in terms of reducing restrictions on work and travel and an overall reduction in the burden of treatment. Conversely, there are patients for whom you would not consider Ravulizumab treatment. Ravulizumab is unlikely to be used as a first line therapy for incident patients with suspected aHUS. Approximately 50% of patients presenting with a suspected diagnosis of aHUS who are treated with Eculizumab withdraw from treatment within the first few weeks of months of treatment either due to identification of an alternative diagnosis or futility In this patient group a long acting complement inhibitor would not be indicated. There may also be a group of patients for whom, once remission after the acute episode has been established, long term treatment will not be required. In this group of patients a long acting complement inhibitor will be of limited or no benefit. Stopping treatment may be a better option.	Thank you for your comment. The challenges of aHUS diagnosis, and the features of ravulizumab treatment response and treatment discontinuation will be considered by the appraisal committee in any future meeting for this appraisal.
	NHS England and Improvement	The population is appropriately defined	Comment noted. No action required.
Comparators	Alexion Pharmaceuticals	We believe the comparator of eculizumab as presented in the draft scope represents current standard of care in the NHS for patients with aHUS.	Comment noted. No action required.

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	UK		
	aHUS alliance Global Action	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?* Yes	Comment noted. No action required.
	British Association for Paediatric Nephrology	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?* Yes	Comment noted. No action required.
	Kidney Research UK	Yes. Eculizumab is the currently the only licenced treatment for aHUS and should be considered as the current standard of care. Although plasma exchange is sometimes initiated for the treatment of aHUS there is evidence that patient outcomes after plasma exchange are inferior when compared to complement inhibition. The morbidity and mortality associated with liver transplantation are too great to consider this as a viable treatment option.	Comment noted. Following the consultation and scoping workshop on the first draft of the scope (January 2020), the current treatment, and appropriate comparator for people who develop aHUS for the first time, was eculizumab.
	NHS England and Improvement	The best alternative treatment is accurately described	Comment noted. No action required.
Outcomes	Alexion Pharmaceuticals UK	We suggest aligning the outcome measures included in the scope to those of the clinical trial programme for ravulizumab which include: Primary endpoint:	Thank you for your comment. The outcomes listed are not

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		• Complete TMA response Secondary endpoints: • Dialysis requirement status • Time to complete TMA response • Complete TMA response status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) • Change from baseline in chronic kidney disease (CKD) stage • Change from baseline in haematologic parameters (platelets, LDH, haemoglobin) • Increase in haemoglobin ≥20g/L from baseline • Change from baseline in quality of life • Adverse events Of the outcomes listed in the draft scope, the following were not captured in the clinical trials: • Overall survival (not captured as an outcome in the clinical trials although deaths were collected in the context of the safety analysis. Overall survival has, however, been modelled in the pharmacoeconomic analyses using ONS data and mortality from the literature) • Disease recurrence (No data available from the clinical trial programme as yet although considered in the pharmacoeconomic analyses with inputs based on longer term eculizumab trials and aHUS registry data. Note: TMA parameters were monitored in clinical trials in patients who discontinued treatment but remained on study and in those who responded to treatment and remained on study, however, no data on recurrence are available as yet based on the limited follow up to date.)	intended to be exhaustive. The NICE Guide to the methods of technology appraisal states that outcomes in the scope should "…measure health benefits and adverse effects that are important to patients and/ or their carers." Also, the way in which the outcome should be measured is not usually specified in the scope. No change required.

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		• Other major non-renal clinical outcomes (Non-renal clinical outcomes assessed include changes from baseline in haematological parameters (platelets, LDH, haemoglobin). No other non-renal clinical outcomes were included as efficacy outcomes in the clinical trial programme, however other major non-renal events such as thrombosis, cardiac events, etc. that occurred during the course of the clinical trials were captured as adverse events.) • Eligibility for/success of transplantation (Not assessed as an outcome in the clinical trials although considered in the pharmacoeconomic analyses. Only patients with CKD stage 5/ESRD are assumed to be eligible for transplant. This transition was informed using literature. Transplant outcomes are informed by registry information on patients treated with eculizumab.)	
	aHUS alliance Global Action	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Comment noted. No action required.
	British Association for Paediatric Nephrology	For children with a chronic disease, the impact on education is important to assess. The reduced frequency of visits compared with eculizumab may result in improved access to education and this should be included. Note that children less than 20kg will remain on 4 weekly visits and over 20kg will be on 8 weekly visits. Chronic illness in children impacts parental employment. The impact on this should also be included.	Thank you for your comment. The potential impact on resource costs and savings is considered from the perspective of the NHS and personal social services. Therefore, the impact on employment is not considered. If evidence is presented, the health impact on both patients and/or

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			their carers can be considered by the committee.
	Kidney Research UK	Yes, the outcomes are appropriate.	Comment noted. No action required.
	NHS England and Improvement	The comparators are appropriate	Comment noted. No action required.
Economic analysis	Alexion Pharmaceuticals UK	A cost-effectiveness analysis will be presented to assess the value of ravulizumab compared with eculizumab in aHUS patients, where differential effectiveness is considered based upon the results of a patient level indirect treatment comparison (ITC) using propensity score weightings. The analysis will be conducted from the NHS perspective with a lifetime horizon and will be based upon an adaptation of the state transition model previously developed for eculizumab and presented to NICE in HST1. In addition, an analysis assuming equal effectiveness will be presented to assess the difference in treatment and management costs for aHUS patients receiving ravulizumab versus eculizumab, based on the lack of any observed significant or systematic differences between treatment arms in the ITC, clinical biological and rationale to support this assumption and the availability of a positive non-inferiority study in PNH. The analysis will be presented from an NHS perspective and will use a lifetime horizon in line with NICE guidance.	Comment noted. No action required.
	aHUS alliance Global Action	No comment	Comment noted. No action required.
	British	No comments on this	Comment noted. No

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	Association for Paediatric Nephrology		action required.
	Kidney Research UK	Yes, the economic analysis is appropriate and in view of the high cost of the current standard of care an important component of the appraisal.	Comment noted. No action required.
	NHS England and Improvement	Would it not also be appropriate to provide an economic analysis if the cost is greater than for technologies recommended in published NICE technology appraisal guidance for the same indication,	Thank you for your comment. The clinical- and cost-effectiveness of ravulizumab relative to eculizumab will be appraised using the framework as set out in the NICE Guide to the methods of technology appraisal.
Equality and Diversity	Alexion Pharmaceuticals UK	We do not envisage any equality issues related to the proposed draft remit and scope.	Comment noted. No action required.
	aHUS alliance Global Action	No comment	Comment noted. No action required.
	British Association for Paediatric Nephrology	I don't think that this remit/scope will result in inequality	Comment noted. No action required.
	Kidney	I do not see any reason why the current scope should lead to inequality.	Comment noted. No

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	Research UK		action required.
	NHS England and Improvement	The reduced frequency of delivery could benefit a group of patients that may often not be able to access medical care well with protected characteristics.	Comment noted. The extent to which a person's disability will affect their ability to receive treatment or the assessment of outcomes will be considered by the committee.
Other considerations	Alexion Pharmaceuticals UK	Two new vial ravulizumab vial sizes at (3mL and 11mL containing 300mg and 1100mg ravulizumab, respectively) at 100mg/mL concentration are currently under regulatory review, with EMA approval anticipated in [redacted]	Comment noted. The committee will consider all licensed doses and formulations.
	aHUS alliance Global Action	None.	Comment noted. No action required.
	British Association for Paediatric Nephrology	Ravulizumab represents a potential benefit to patients with aHUS and the NHS, in particular in reducing the number and frequency of healthcare treatment episodes and improving quality of life. The diagnosis of aHUS is complex, requires exclusion of several differential diagnoses and is guided by the aHUS national service. Due to the acute and life/kidney-threatening nature of the disease, treatment with eculizumab may be commenced whilst awaiting results of numerous investigations. If the diagnosis of aHUS can be excluded because an alternative diagnosis is subsequently reached, eculizumab therapy can be discontinued after a small number of doses. The use of a longer acting agent would not seem	Comment noted. The benefits of ravulizumab will be appraised using the framework as set out in the NICE Guide to the methods of technology appraisal. Challenges relating to achieving an accurate aHUS diagnosis will be taken in consideration.

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		appropriate until the need for ongoing treatment is fully established.	
	Kidney Research UK	The panel should consider when Ravulizumab will be used, specifically in which patient groups it will be used and in which stage of their treatment pathway. Ravulizumab is unlikely be the first line treatment for all patients presenting with suspected aHUS. A proportion of patients who do start treatment will withdraw from treatment. However, some will require ongoing, long-term treatment and it is this group of patients who will be candidates for Ravulizumab treatment.	Comment noted. NICE will appraise the technology within its marketing authorisation. The appraisal committee will consider any evidence presented relating to the ravulizumab long-term usage and discontinuations.
	NHS England and Improvement	No additional considerations	Comment noted. No action required.
Innovation	Alexion Pharmaceuticals UK	Ravulizumab addresses some remaining areas of unmet need in the management of patients with aHUS. Ravulizumab provides immediate, complete and sustained terminal complement inhibition across an 8-week dosing interval, reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase, compared with the 26 needed for effective eculizumab treatment which has a 2-week dosing interval. This could result in a reduced interruption of patients' weekly routines including education and/or employment. The need for frequent infusions also puts patients' veins at risk of long-term damage and can result in a need for venous access ports in some patients, especially children, which subsequently puts them at risk of port-related complications.(5) There are also benefits to the NHS of fewer infusion procedures required with	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.

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		ravulizumab over eculizumab in the approximately 50% of patients who receive their treatment in the hospital setting. This is especially relevant in an environment with Covid-19 where reducing the frequency of hospital attendance for patients is of particular value.	
	aHUS alliance Global Action	Yes, although the active ingredient of the technology is as clinically effective as its predecessor, the considerable reduction in patients' treatment obligation is a step increase in their quality of life.	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.
	British Association for Paediatric Nephrology	This is an incremental change in the management of patients with atypical HUS rather than the step change that was achieved with eculizumab. The innovation is to increase the half-life to reduce dosing frequency. The less frequent dosing requirement is likely to be beneficial to patients in whom an ongoing requirement for anti-complement treatment is established. The biggest impact of this technology is to reduce the burden of treatment visits on patients, families and the NHS. For a sub-group of patients this is likely to make a big impact.	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.
	Kidney Research UK	There is a already a very effective treatment for aHUS. It is unlikely that Ravulizumab will be more effective than the current standard of care (Eculizumab) in terms of induction or maintenance of remission. Ravulizumab targets the same complement protein as Eculizumab. Ravulizumab is a modified form of Eculizumab which has been engineered to dissociate from its target at low pH. This leads to recycling of internalised antibody, therefore increasing its half-life. This is innovative monoclonal antibody technology.	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the

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		The increased half-life reduces the dosing frequency. This will lead to a reduction in health care costs. Both Eculizumab and Ravulizumab are administered intravenously. The reduced frequency of administration will have a positive impact on quality of life. This represents a significant benefit for patients, particularly if intravenous access is difficult (children and some adults). Feedback from eligible patients, collected by KRUK, emphasises the importance of reduced dosing frequency (see comments in appendix). This will provide greater flexibility around work and particularly travel, which is significantly restricted by infusions every two weeks. This not only affects the patient but whole families. Intravenous infusions are unpleasant for patients and reducing the number required will be welcomed. This data should be collected and considered in the QALY analysis.	technology. The potential impact on resource costs and savings is considered from the perspective of the NHS and personal social services. Therefore, the impact on employment is not considered. If evidence is presented, the health impact on both patients and/or their carers can be considered by the committee.
	NHS England and Improvement	Other treatment options are available for this patient group. We would therefore not consider this treatment option to be a step change.	Comment noted. No action required.
Questions for consultation	Alexion Pharmaceuticals UK	**Q:** Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately? **A:** Subgroup analyses of primary efficacy by age, gender, ethnicity, geographic region, transplant history, immunogenicity status and dialysis status at baseline were conducted within the clinical trials. We do not anticipate there will be any particular subgroups in whom the technology is expected to provider significantly greater benefits or value for money. **Q:** To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into	Comment noted. NICE will appraise the technology within its marketing authorisation. Subgroups will be considered on the basis that clinical or cost-effectiveness may differ from the overall population.

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		practice? **A:** We do 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 provision of eculizumab within the NHS.	Comment noted. No action required.
	aHUS alliance Global Action	No comment	Comment noted. No action required.
	NHS England and Improvement	No additional comments.	Comment noted. No action required.
Additional comments on the draft scope	Alexion Pharmaceuticals UK	None.	Comment noted. No action required.

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

None