National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Alexion	Yes, we believe it is appropriate to refer ravulizumab for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) to NICE for evaluation via the Highly Specialised Technologies (HST) process.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	Aplastic Anaemia Trust	The patient community welcomes access to this treatment and potential for improved quality of life, due to 8-weekly 4administration.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	PNH Support	Patients are keen to access this treatment and be able to live much more independent and productive lives through only having 8 weekly infusions (compared to the current 2 weekly infusions with Eculizumab).	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	PNH NHSE-funded National Service - Leeds	It is entirely appropriate and important that NICE evaluates ravulizumab for PNH.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
Wording	Alexion	Yes	Comment noted. No change to the scope required.

Section	Consultees	Comments	Action
	PNH NHSE-funded National Service - Leeds	The remit does not exactly match the licence for ravulizumab. The evaluation should be for patients with PNH with haemolysis with clinical symptom(s) indicative of high disease activity. This is best defined as the NHSE criteria for the use of eculizumab in PNH. (https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf)	Comment noted. The remit is kept broad but the technology will be appraised within its marketing authorisation. No change to the scope required.
Timing Issues	Aplastic Anaemia Trust	Accelerated access to this therapy would be hugely welcome by the patient community. The availability of this treatment and its vastly improved efficiency of administration (8-weekly) would alleviate the stress on the NHS resources which are already at breaking point.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	Alexion	The scoping process for ravulizumab for the treatment of PNH has been subject to an unacceptable 14 month delay at NICE, for which no explanation has been provided. Ravulizumab, which received European Marketing Authorisation for the treatment of PNH in July 2019, addresses several areas of unmet need in the management of patients with PNH and also has the potential to deliver cost savings to NHS England compared with eculizumab. It is imperative therefore that this re-scope exercise and subsequent NICE appraisal is completed according to due process and in a timely manner to provide NHS England with appropriate guidance to inform its national commissioning decisions.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	PNH Support	Patients are keen to access this treatment as soon as possible and be able to live much more independent and productive lives through only having 8 weekly infusions. This will in turn free up NHS resource currently committed to the management and oversight of the 2 weekly Eculizumab infusions.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.

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	PNH NHSE-funded National Service - Leeds	Patients with PNH are currently treated with eculizumab. There has been a prolonged delay in the evaluation of ravulizumab. It is urgent to resolve this.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
Additional comments on the draft remit	Aplastic Anaemia Trust	Upfront assurance is needed that a relatively small population of patients affected, will not in any way hamper the process and enable access to this much-needed therapy.	Comment noted. This evaluation has been scheduled in the Highly Specialised Technologies work programme, which considers drugs for very rare conditions.
	PNH NHSE-funded National Service - Leeds	The remit fails to recognise that eculizumab is funded in England by NHSE for all patients with PNH fulfilling the criteria of high disease activity since 2008.	Comment noted. The remit outlines the disease, the patients and the technology that will be covered by the evaluation. No change to the scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Aplastic Anaemia Trust	Aplastic anaemia (AA) is a rare illness of the immune system, whereby the bone marrow fails, destroying stem cells, thus halting the production of vital red, white blood cells and platelets. This affects people's ability to function – they may bleed simultaneously, bruise, attract life-threatening infections and are haunted by extreme fatigue. If untreated, people die quickly. Treatment closely resembles that of cancer patients, and will be prolonged, costly and with severe side effects in a lot of patients. The only curative treatment currently is a stem cell transplant, however, this will not be a suitable treatment option for a large proportion of patients. Aplastic anaemia is intrinsically linked to Paroxysmal Nocturnal Haemoglobinuria (PNH). There is strong evidence to indicate that all patients with PNH have an underlying bone marrow failure, usually aplastic anaemia, either preceding or coexistent with the diagnosis of PNH (Rotoli et al, 1982; Rotoli & Luzzatto, 1989; Maciejewski et al, 1997). Whilst the 'PNH clone' does not have any 'malignant' tendency, however, it expands if there is a selective advantage for it to do so (Rawstron et al, 1999) as described in aplastic anaemia patients that develop PNH (Tichelli et al, 1988; Schrezenmeier et al, 1995). "PNH only arises in the background of bone marrow failure syndromes, the most common being aplastic anaemia. That means that these two diseases are very closely linked. In fact, you cannot have PNH without having AA. Both can be very severe and life threatening with huge mortality. Supporting patients undergoing treatment for both illnesses is therefore crucial." Dr Anita Hill, Lead Consultant for National PNH Service, Leeds, Englandcom	Comment noted. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. No change to the scope required.

Section	Consultees	Comments	Action
	Alexion	We suggest removing the word 'alternative' from the following sentence: *'The number of patients treated with alternative complement inhibitor eculizumab in the UK as of December 2018 was 239.'* In addition to presenting patient survival data without treatment, we believe it would present a more rounded picture to also include survival for patients treated with eculizumab, for example: *Several studies have evaluated survival in eculizumab treated PNH patients[1] showing a similar survival compared to normal (non-PNH) matched controls[2] (Kelly et al., 2011) or an improved survival compared to untreated PNH patients[2].[3]* In addition, the background section states that there is currently no NICE guidance for treating PNH. While this is indeed the case, it is a function of the fact that at the time of marketing authorisation of eculizumab, NICE was not undertaking evaluations of technologies for ultra-orphan conditions. As such, eculizumab underwent an alternative route of assessment of appropriateness for use in the NHS and was approved for routine commissioning as outlined in the NHS England Service Specification 'Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents)'[4] We therefore believe additional text should be added to the background section to reflect the above.	Comments noted. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The scope has been updated to reflect some of the comments.

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	PNH NHSE-funded National Service - Leeds	The assessment of survival of PNH without eculizumab uses a reference that is not appropriate. The statement that "Ten-year survival after diagnosis and without treatment with a complement-inhibitor has been estimated to range between 65% and 78%." is not accurate. The more accurate figure is that the 10 year survival in PNH is approximately 50%. The most appropriate reference in the pre-eculizumab era is: Hillmen P, Lewis SM, Bessler M, Luzzatto L and Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. 1995 *New England Journal of Medicine,* 333, 1253-1258.	Comment noted. The background section has been updated.
The technology/ intervention	Alexion	We suggest amending the sentence: 'It is administered by intravenous infusion' by adding to the end of the sentence 'every 8 weeks during maintenance treatment'	Comment noted. The technology section of the scope briefly describes the technology of interest and does not usually include details of dosing. No change to the scope required.
	PNH NHSE-funded National Service - Leeds	The description of the technology is correct but fails to mention the key advantages of ravulizumab compared to the standard of care, eculizumab. These are that ravulizumab is only delivered once every 8 weeks compared to once every two weeks. This has major potential advantages for the NHS as well as for patients. Secondly approximately 20% of patients on eculizumab require a higher dose which is not necessary for ravulizumab.	Comment noted. The technology section of the scope briefly describes the technology of interest and does not usually include details of dosing. No change to the scope required.
Population	Alexion	The population presented reflects the licensed indication for ravulizumab in PNH. However, we believe the population would be more accurately reflected by stating: 'Adults with paroxysmal nocturnal haemoglobinuria who meet the criteria for complement-inhibitor treatment as outlined in the NHS England Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents) Service Specification.'[4]	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.

Section	Consultees	Comments	Action
	PNH Support	Ravulizumab may be most appropriate for treating a subset of patients with PNH i.e. adults who respond well to a C5 inhibitor and don't have additional unmet need i.e. extra-vascular haemolysis.	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
	PNH NHSE-funded National Service - Leeds	The population is appropriate but is not clearly defined. This should follow the NHSE approved indications for eculizumab in PNH. (https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf)	Comment noted. The technology will be appraised within its marketing authorisation. No change to the scope required.
Comparators	Aplastic Anaemia Trust	We feel that the comparator being 'Best supportive care' is not appropriate. This should be Eculizumab.	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.

Section	Consultees	Comments	Action
	Alexion	No, the comparator of best supportive care is not the standard treatment currently used in the UK. Eculizumab is the current standard of care in UK clinical practice for patients with PNH who require treatment. As such, eculizumab is the appropriate comparator for ravulizumab. Even though there has been no NICE appraisal of eculizumab for PNH, NICE states that comparators can also be considered when: '…a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so **embedded in clinical practice** that its use will continue unless and until it is replaced by a new technology.' Eculizumab is routinely commissioned as set out in the NHS England Service Specification 'Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents)': 'Eculizumab is a life-changing therapy in haemolytic PNH which is effective in almost all such patients and was therefore commissioned through NHS England in 2008.' [4] Best supportive care is not considered a relevant comparator for ravulizumab as all patients in the intended target population receive eculizumab in current practice.	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.

Section	Consultees	Comments	Action
	PNH Support	The standard treatment is Eculizumab and not “best supportive care”.	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.

Section	Consultees	Comments	Action
	PNH NHSE-funded National Service - Leeds	The described comparator “Best Supportive Care” is wholly inappropriate. Best supportive care for this group of patients with high disease activity has not been the standard of care in England since 2008 when eculizumab was commissioned by the NHS. Since then all patients fulfilling the clinical criteria for high disease activity have been treated with eculizumab. This is clearly the standard of care and has to be the key comparator. All major healthcare systems globally have approved eculizumab for this patient population and this is the only appropriate comparator for ravulizumab. Eculizumab was listed in the original NICE scoping for ravulizumab in September 2018 (https://www.nice.org.uk/guidance/gid-hst10023/documents/draft-scope-pre-referral). Why has this been removed?	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.
Outcomes	Aplastic Anaemia Trust	We welcome the positive benefits access to Ravulizumab would bring. The ability to only have to the drug administered 8-weekly has huge benefits to the patients’ physical and mental well-being. We anticipate the impact on the broader quality of life to be very positive – more freedom by the patients’ families to plan for longer holidays, increased access to employment, looking after older relatives. The broader economic benefit to society of enabling more PNH patients to access employment cannot be under-estimated. The draw on NHS nurses to administer the treatment will reduce.	Comments noted. No change to the scope required.
	Alexion	Yes	Comments noted. No change to the scope required.

Section	Consultees	Comments	Action
	PNH Support	Under “Impact of the technology beyond direct health benefits,” we comment that: as this therapy is delivered intravenously every 2 months compared to Eculizumab (which should be the comparator) which is delivered intravenously every 2 weeks, patients are not reminded that they have PNH for 2 months at a time which has a significant psychological impact. Two monthly infusions also permit less disruption to patients’ and carers’ employment and associated issues and family life generally. Patient access to treatment with Ravlizumab’s 8 weekly infusions will free up NHS resource currently committed to the management and oversight of the 2 weekly Eculizumab infusions.	Comments noted. The committee will consider all potential benefits of the technology throughout the course of the evaluation. No change to the scope required.
	PNH NHSE-funded National Service - Leeds	The outcomes listed are appropriate for this evaluation.	Comment noted. No change to the scope required.
Equality and Diversity	Alexion	We do not envisage any equality issues related to the proposed draft remit and scope	Comment noted. No change to the scope required.
	PNH Support	Age and pregnancy are protected characteristics and if different recommendations are made for children, adults and pregnant women, this could lead to inequality. We do not believe Ravulizumab has not been licenced for under 18 year olds.	Comment noted. The impact of any recommendation for ravulizumab on groups of people with protected characteristics will be considered by the committee. No change to the scope required.
	PNH NHSE-funded National Service - Leeds	The standard of care for PNH is eculizumab which is given every two weeks by intravenous infusion. This is burdensome for patients whereas ravulizumab is given every 8 weeks. Vulnerable patients, for example elderly patients, find the less frequent infusions more manageable.	Comment noted. The impact of any recommendation for ravulizumab on groups of people with protected characteristics will be considered by the committee. No change to the scope required.

Section	Consultees	Comments	Action
Innovation	Alexion	Ravulizumab is an innovative treatment developed to address several areas of unmet need in the management of patients with PNH. In non-inferiority, head-to-head trials of ravulizumab and eculizumab, ravulizumab achieved immediate, complete and sustained C5 inhibition, maintained efficacy and continuous disease control compared with the current standard of care, eculizumab. In addition, compared to the 2-weekly eculizumab regimen, the 8-weekly ravulizumab regimen lessens the treatment burden for patients by reducing the number of infusions from 26 per year to 6 per year, which could result in a reduced interruption of weekly routines including education and/or employment.	Comment noted. The potential innovative nature of ravulizumab will be considered by the committee throughout the evaluation. No change to the scope required.
	PNH Support	The length of time between infusions (8 weeks) for this therapy allows patients (and carers) an increased quality of life, increased psychological wellbeing and less interruptions to patients' and carers' employment and family life generally compared to 2 weekly infusions of Eculizumab. Venous access every 8 weeks rather than every 2 weeks is also a benefit as damage to veins can be mitigated.	Comment noted. The potential innovative nature of ravulizumab will be considered by the committee throughout the evaluation. No change to the scope required.
	PNH NHSE-funded National Service - Leeds	Yes ravulizumab is an innovative therapy compared to eculizumab with the potential to have significant and substantial health-related benefits. If ravulizumab is compared to "Best Supportive Care" then ravulizumab will prevent the deaths of half of the patients with PNH in the evaluation.	Comment noted. The potential innovative nature of ravulizumab will be considered by the committee throughout the evaluation. No change to the scope required.

Section	Consultees	Comments	Action
Other considerations	Aplastic Anaemia Trust	We need assurance that there is some weighting attached to the cost vs benefit assessment, to take into account the rarity of the condition.	Comment noted. As described in the Highly Specialised Technologies process guide, paragraphs 46, 53 and 54, when considering the overall health benefits, the Evaluation Committee can accept analysis that explores a QALY weighting that is different from that of the reference case in some circumstances.
	Alexion	None	No change to the scope required.
	PNH NHSE-funded National Service - Leeds	The National-funded PNH service arranges for the infusion of eculizumab every two weeks. This is difficult leading to a high dependence for patients. Moving to ravulizumab would be far more convenient for patients and would take a significant strain off the NHS. This has been even more apparent during the COVID-19 pandemic during which the delivery of 2 weekly infusions is proving to be very challenging.	Comment noted. No change to the scope required.

Questions for consultation	Alexion	**Questions:** **Q:** Have all relevant comparators for ravulizumab been included in the scope? **A:** No. As described above eculizumab is the only appropriate comparator for ravulizumab in the target PNH patient population. **Q:** Which treatments are considered to be established clinical practice in the NHS for PNH? **A:** Eculizumab is the only established treatment for PNH patients who require treatment in current UK clinical practice. All patients who are considered candidates for treatment receive eculizumab. Eculizumab is indicated in adults and children for the treatment of: - Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. The NHS England Service Specification states that 'Eculizumab is the first-line treatment for patients with PNH if they meet any one of the following conditions (as set out in the NHS England Service Specification for Paroxysmal Nocturnal Haemoglobinuria)[6]: • Thrombosis related to PNH • Complications associated with haemolysis: i. Renal failure ii. Pulmonary hypertension • Pregnancy (and for at least 3 months post-partum) • Haemolytic (LDH >1.5xULN) symptomatic PNH with **either** of the following: i. Anaemia (Hb <9g/L) or ii. Agreement with Joint Service colleagues at MDT that the patient should receive treatment • Exceptional cases in whom eculizumab is considered appropriate (not fulfilling the above criteria) will be approved through discussion between the 2 Nationally	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.

Section	Consultees	Comments	Action
		Commissioned PNH Services and the National Commissioner' **Q:** How should best supportive care be defined? **A:** As detailed above, best supportive care is not an appropriate comparator for ravulizumab in PNH. The intended target patient population for ravulizumab is the same PNH population as is eligible for treatment with eculizumab. As such, eculizumab is the appropriate comparator for ravulizumab in PNH. **Q:** Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or value for money, or other groups that should be examined separately? **A:** The only subgroup of patients in whom ravulizumab may provide greater clinical benefits or more value for money are those patients who are currently receiving higher than label dosing of eculizumab. However, there are no data from clinical trials in this population at present, therefore separate examination of this population is not feasible at this time. **Q.** Appropriateness of the Highly Specialised Technologies Programme to evaluate ravulizumab. **A.** The HST route is appropriate for ravulizumab as ravulizumab treats an ultra-orphan condition – PNH, and the technology meets all of the criteria for prioritisation for appraisal through the HST process[7]	Comment noted. No change to the scope required. Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.
	PNH NHSE-funded National Service - Leeds	It is now 18 months since NICE's initial scoping for ravulizumab for PNH. Ravulizumab is more convenient and almost certainly less expensive than eculizumab and the delay in appraising ravulizumab has meant that patients in other European and North American countries have had access to ravulizumab whereas patients in England do not understand why they cannot benefit from this technology. Further delay is not acceptable.	Comment noted. This evaluation has been scheduled into the Highly Specialised Technologies work programme.

Section	Consultees	Comments	Action
Additional comments on the draft scope	Alexion	None **References** 1 Hillmen P et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2013;162:62–73. 2 Kelly RJ, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 2011; 117:6786-6792. 3 Loschi M, et al. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. American Journal of Hematology 2016; 91:366-370 4 NHS England Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents) Service Specification. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/08/Paroxysmal-nocturnal-haemoglobinuria-service-adult-and-adolescent.pdf 5 NICE Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [6] NHS England Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents) Service Specification. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/08/Paroxysmal-nocturnal-haemoglobinuria-service-adult-and-adolescent.pdf [7] NICE Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf	No change to the scope required.

Section	Consultees	Comments	Action
	PNH NHSE-funded National Service - Leeds	We would like to re-iterate that “Best Supportive Care” is not an appropriate comparator for ravulizumab in PNH. The gold-standard of care in England since 2008 has been eculizumab. Eculizumab was listed in the original NICE scoping for ravulizumab in September 2018 (https://www.nice.org.uk/guidance/gid-hst10023/documents/draft-scope-pre-referral). Why has this been removed?	Comment noted. Eculizumab is commissioned for this indication by NHS England through the national PNH highly specialised service. As such, eculizumab has not been through a health technology assessment, and the current value of eculizumab to the NHS has not been evaluated. Therefore, if ravulizumab were to be recommended for NHS use on the basis of comparing ravulizumab with eculizumab, this could lead to an unacceptable use of NHS resources. No change to the scope.

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

None