National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Emapalumab for treating primary haemophagocytic lymphohistiocytosis [ID1438]

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

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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Novimmune S.A.	'Would it be appropriate to refer this topic to NICE for evaluation?' - Yes. Novimmune agrees that this topic is appropriate for appraisal and welcomes the opportunity to discuss the process under which NICE will appraise emapalumab.	Comment noted. No action required.
	Genetic Alliance UK	This medicine is a treatment for a very care condition involving a high level of unmet need, a fact which has been recognised by the European Medicines Agency in granting the treatment access the PRIME scheme. We consider that this is an appropriate topic for the HST programme.	Thank you for your comment. The topic will not be evaluated as an HST because emapalumab does not meet all of the criteria needed for selection into the HST work programme (i.e. exclusive use in the context of a highly specialised service,

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			potential for life-long use, and significant need for national commissioning).
	Royal College of Pathologists and the British Society for Haematology	'Would it be appropriate to refer this topic to NICE for evaluation?' - Yes	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	This proposed treatment is entirely appropriate for NICE evaluation.	Comment noted. No action required.
	Primary Immunodeficiency UK	'Would it be appropriate to refer this topic to NICE for evaluation?' - Yes. HLH is a serious, life-threatening, rare condition. Having new ways to manage the over-activated immune system and the limit tissue damage it causes are needed.	Comment noted. No action required.
Wording	Novimmune S.A.	'Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?' - Yes	The remit has been amended in line with the standard wording for single technology appraisals.
	Genetic Alliance UK	This is the standard wording.	The remit has been amended in line with the standard wording for single technology appraisals.

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	Histiocytosis UK (Histio 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?' - Yes	The remit has been amended in line with the standard wording for single technology appraisals.
	Primary Immunodeficiency 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?' - Yes	The remit has been amended in line with the standard wording for single technology appraisals.
Timing Issues	Novimmune S.A.	Emapalumab expects to receive marketing authorisation approval by the EMA in [redacted] (EMA submission: July 2018; evaluation under PRIME). Emapalumab offers a treatment option in an extremely compromised patient population of very young children, who have failed standard of care and for whom there are currently no licensed treatment options. We request that NICE considers emapalumab in light of this unmet medical need, to identify a route for emapalumab to reach patients in NHS England as close as possible to marketing authorisation approval.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
	Genetic Alliance UK	Although the marketing authorisation application for this medicine has not yet been submitted to the EMA, we understand that it is expected shortly. Since the medicine has been granted accelerated assessment by the EMA under the PRIME scheme, this scoping process is timely as it is important that patients in the UK are able to access the treatment as soon as possible after a license is granted.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has

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			scheduled this topic into its work programme.
	Histiocytosis UK (Histio UK)	Additional treatment options are badly needed for patients with primary HLH to control disease prior to HSCT, therefore we would consider this evaluation urgent.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
	Primary Immunodeficiency UK	Given the severity and seriousness of HLH, its poor survival rates and associated health complications this evaluation should be treated as urgent.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

Comment 2: the draft scope

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Background information	Novimmune S.A.	Please consider the following changes in the background information (in track changes): • "Excessive activation of specific white blood cells, including histiocytes (macrophages) and lymphocytes (specifically T cells, B cells and Natural Killer [NK] cells) and an associated increase in the level of the ~~chemical~~ cytokine interferon gamma (IFNγ) leads to overproduction of downstream pro-inflammatory cytokines and a hyperinflammatory syndrome." • "The overactivation of the immune system causes fever, enlargement and damage to the liver and spleen, while the hemaphagocytosis ~~it also~~ destroys blood ~~producing~~ cells in the bone marrow, resulting in ~~As a result, people have~~ low numbers of red blood cells (anemia) and a reduction in the number of platelets, which may cause abnormal bleeding." • "The ~~brain~~ CNS may also be affected, causing impaired muscle coordination, paralysis, blindness and coma." • "Without treatment the median survival of patients with primary HLH is less than 2 months~~time ranges from 2 to 6 months~~; with treatment survival is 55% at 3 years[2]" -Please note that with respect to survival, the Henter et al 2002 study only quotes Janka 1983, where it is reported that without treatment the median survival of primary HLH is less than 2 months. • "The incidence of primary HLH is estimated to ~~be~~ range between 1.2-1.5 per million[3] children aged less than 15 years (Meeths et al., 2015)". - Please note that the number of children (0-18 years) diagnosed with primary HLH in England needs to be recalculated based on this figure. • *Henter, J. I., A. Samuelsson-Horne, M. Arico, R. M. Egeler, G. Elinder, A. H. Filipovich, H. Gadner, S. Imashuku, D. Komp, S. Ladisch, D. Webb, and G. Janka. 2002. 'Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation', Blood, 100: 2367-73* • *Janka, G. E. 1983. 'Familial hemophagocytic lymphohistiocytosis', Eur J Pediatr, 140: 221-30.*	Thank you for your comment. The background section of the scope has been amended. Untreated survival range amended in line with comments from consultation, treated survival estimate removed as not relevant information.

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		• *Meeths, M., A. Horne, M. Sabel, Y. T. Bryceson, and J. I. Henter. 2015. 'Incidence and clinical presentation of primary hemophagocytic lymphohistiocytosis in Sweden', Pediatr Blood Cancer, 62: 346-52.*	
	Genetic Alliance UK	In paragraph four of the background section, the word prevalence has been used mistakenly to refer to the number of diagnoses per year. This should instead read incidence. We understand that the estimate of survival with treatment comes from international treatment guidelines produced by the Histiocyte Society in 1994. Survival rates are likely to have increased somewhat since then, in part due to improvements in haematopoietic stem cell transplantation.	Thank you for your comment. The background section of the scope has been updated based on available incidence data.
	Royal College of Pathologists and the British Society for Haematology	'Consider the accuracy and completeness of this information'. - Adequate	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	Patients tend to become neutropaenic as well as anaemic and thrombocytopaenic leaving them susceptible to further infections. They also suffer seizures as a manifestation of CNS disease. Forms of primary HLH are inherited in various genetic manners not just in an autosomal recessive fashion.	Thank you for your comment. The background section of the scope has been amended.
	Primary Immunodeficiency UK	Patient numbers: We are not aware of a patient registry to check the prevalence rate quoted. HLH is difficult to diagnose because symptoms mimic severe infection or other conditions. Therefore, it is likely to be under diagnosed.	Thank you for your comment. The background section of the scope has been updated based on available incidence data.

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The technology/ intervention	Novimmune S.A.	Please consider the following changes in the description of the technology (in track changes): • Emapalumab (Gamifant, NovImmune) is a fully human anti-interferon gamma (IFNγ) monoclonal antibody (mAb) that binds to and neutralises ~~targets interferon gamma (~~IFNγ~~)~~. IFNγ is a cytokine secreted by cells of the immune system to help regulate immune functions. Emapalumab is specifically developed for HLH and it is administered as an intravenous infusion It has been studied in clinical trials, in people up to 18 years of age with a confirmed or suspected diagnosis of primary HLH.	Thank you for your comment. This section provides a brief overview of the technology. Further details may be discussed by the committee during the appraisal. Consultees confirmed that the population will include primary haemophagocytic lymphohistiocytosis, therefore no change to the wording of the population is needed.
	Royal College of Pathologists and the British Society for Haematology	'Is the description of the technology or technologies accurate?' - Yes	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	Yes, although you could expand to clarify that in HLH there is overproduction of cytokines including IFN-gamma and this antibody acts to counteract the excessive production and subsequent tissue damage.	Thank you for your comment. This section provides a brief overview of the technology. Further details may be

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			discussed by the committee during the appraisal.
	Primary Immunodeficiency UK	'Is the description of the technology or technologies accurate?' - Yes	Comment noted. No action required.
Population	Novimmune S.A.	Please consider the following changes (in track changes): People with primary and suspected primary haemophagocytic lymphohistiocytosis aged up to 18 years.	Thank you for your comment. Consultees confirmed that the population will include primary haemophagocytic lymphohistiocytosis, therefore no change to the wording of the population is needed.
	Genetic Alliance UK	We understand that the incidence data used (1.2 per million children) is believed likely to be an underestimation, coming from a retrospective study from Sweden published in 1991 where many diagnoses were only made after death. Emapalumab has been studied both as a first line treatment as well as in patients for whom the current standard of care has failed or was unable to be tolerated. It may be appropriate to consider these two groups separately as cost effectiveness may differ. Additionally, we understand that some patients with relapsing or refractory disease may be treated with emapalumab for longer than the standard four to twelve weeks, and should possibly also be examined separately.	Comment on limitations of incidence data noted. If evidence allows, previously untreated and treated subgroups will be considered by the appraisal committee.

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	Royal College of Pathologists and the British Society for Haematology	Appropriate for the studies performed	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	'Is the population defined appropriately? Are there groups within this population that should be considered separately?' - Yes	Comment noted. No action required.
	Primary Immunodeficiency UK	Secondary HLH, associated with the conditions XLP and XIAP may also benefit from this treatment.	Thank you for your comment. Emapalumab will be appraised within its marketing authorisation.

Comparators	Novimmune S.A.	Please consider the following comments with respect to the comparators:
		• The treatments listed in the comparators field of the draft scope are administered as combination treatments based on the HLH94/04 protocols:
		  • HLH-94 protocol is based on initial treatment with glucocorticoids (dexamethasone) and etoposide, plus intrathecal methotrexate in the case of CNS involvement (Henter et al., 2002).
		  • The HLH-2004 protocol added cyclosporine A to the initial treatment (Henter et al., 2007)
		• These HLH protocols should be considered as the comparators for emapalumab; they are the treatments that could be considered as "best alternative care", i.e. emapalumab will displace these protocols not HSCT.
		• *Henter, J. I., A. Samuelsson-Horne, M. Arico, R. M. Egeler, G. Elinder, A. H. Filipovich, H. Gadner, S. Imashuku, D. Komp, S. Ladisch, D. Webb, and G. Janka. 2002. 'Treatment of hemophagocytic*
			Thank you for your comment. HSCT has been removed from the list of comparators.

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		lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation', Blood, 100: 2367-73 • *Henter, J. I., A. Horne, M. Arico, R. M. Egeler, A. H. Filipovich, S. Imashuku, S. Ladisch, K. McClain, D. Webb, J. Winiarski, and G. Janka. 2007. 'HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis', Pediatr Blood Cancer, 48: 124-31.*	
	Royal College of Pathologists and the British Society for Haematology	'Is this (are these) the standard treatment(s) currently used with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?' - Suitable.	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	We would not consider HSCT as an alternative, rather Emapalumab would be used prior to transplant to control disease. Other standards therapies listed would be considered alternatives. For primary HLH patients would still progress to HSCT as a curative treatment option. We would anticipate that this therapy would improve disease remission and allow patients to enter transplant in a better clinical condition, leading to a better transplant outcome.	Thank you for your comment. Consultees noted that emapalumab will not be used as an alternative to HSCT, therefore it has been removed from the list of comparators.
	Primary Immunodeficiency UK	Alemtuzumab (CAMPATH) is also used to regulate immune system. Antibiotics and other antimicrobials are used to treat infections. Treatment overall is intensive. Side effects must be managed carefully and treatments are personalised.	Thank you for your comment. The comparators include chemotherapy, which may include treatments such as alemtuzumab where they are part of established clinical management.

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Outcomes	Novimmune S.A.	Please consider the following changes in the outcomes: Replace “use of steroids” with “glucocorticoid tapering”	Thank you for your comment. Glucocorticoid tapering will be captured within the outcome ‘use of steroids’.
	Genetic Alliance UK	Due to the many clinical forms of the condition it will be important for ‘response’ to be considered quite broadly, referring to improvements in a number of clinical signs and laboratory markers, in order to adequately reflect clinically and psychosocially significant improvements in a patient’s condition. It will be important to consider outcomes over a sufficiently long period of time, at least until a year after haematopoietic stem cell transplantation or last infusion, to fully capture the benefits of treatment. This is because a key potential benefit to this treatment is to improve disease control before haematopoietic stem cell transplantation, with poor disease control associated with higher transplant related mortality.	Thank you for your comment. Details of the definitions and elements of ‘response’ may be explored by the committee during the appraisal. It is expected that outcomes will be considered over a sufficient period to fully capture the effects of the intervention and the comparator.
	Royal College of Pathologists and the British Society for Haematology	‘Will these outcome measures capture the most important health related benefits (and harms) of the technology?’ - Appropriate	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	One could consider survival to HSCT as an outcome	Thank you for your comment. Survival to HSCT has been added

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			to the scope as an outcome.
	Primary Immunodeficiency UK	'Will these outcome measures capture the most important health related benefits (and harms) of the technology?' - Yes	Comment noted. No action required.
Equality and Diversity	Novimmune S.A.	No impact on equality is expected. Please note that in Appendix B, there is a typo (bullet point at the bottom of p. 4): *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ~~eteplirsen~~ emapalumab will be licensed*	Thank you for your comment.
	Royal College of Pathologists and the British Society for Haematology	No change required	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	No concerns	Comment noted. No action required.
	Primary Immunodeficiency UK	Not all HLH patients may be appropriate candidates for HSCT due to extent of tissue damage, lack of suitable donor (minority ethnic groups) etc. In these situations, Emapalumab may offer a vital long-term way of managing the condition.	Comment noted. If the availability of suitable stem-cell donors is lower in specific groups, or for people where a HSCT is unsuitable, the committee should give

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			consideration to the effectiveness of current treatments and should consider whether its recommendations disadvantage such groups.
Other considerations	Novimmune S.A.	No comments.	Comment noted. No action required.
	Royal College of Pathologists and the British Society for Haematology	None suggested	Comment noted. No action required.
Innovation	Novimmune S.A.	This question is appropriate to be included in the scope as we consider emapalumab will be a step change in the management of HLH. We believe that it is an innovative technology as it provides a therapeutic option in an extremely compromised patient population of very young children with no other licensed treatments, it offers a survival benefit and more favourable toxicity profile with none of the safety signals commonly associated with currently available (unlicensed) treatments.	Comment noted. No action required.
	Royal College of Pathologists and the British Society for Haematology	'Do you consider the technology 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)?' - Yes	Comment noted. No action required.

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	Histiocytosis UK (Histio UK)	This treatment has the potential to make a significant difference and substantial impact to the care of patients with primary HLH and improve overall outcome and quality of life.	Comment noted. No action required.
	Primary Immunodeficiency UK	Emapalumab is not a cure but would be an important part of an armoury of treatments to dampen down the immune system in HLH thereby limiting tissue damage to liver, spleen and bone marrow. Limiting tissue damage means that curative HSCT has a better chance of success. Managing immunosuppressant treatment in the context of a prospective HSCT is a difficult balancing act.	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it.
Questions for consultation	Novimmune S.A.	These questions are appropriate to be included in the scope and will be answered in the submission dossier for emapalumab.	Comment noted. No action required.
	Royal College of Pathologists and the British Society for Haematology	No additional	Comment noted. No action required.
	Primary Immunodeficiency UK	Use of any immunosuppressant in HLH need to be carefully managed. Dampening down the immune system too much may leave the patient vulnerable to infection. People affected by HLH are seen by haematologists and immunologists. Care co-ordinated by specialist centres e.g. GOSH, Newcastle have particular expertise in HSCT for HLH. Centres treating HLH patients listed at https://www.histiouk.org/uk/	Thank you for your comment. No action required.

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Additional comments on the draft scope	Novimmune S.A.	Please consider the following addition in the "Nature of the condition" section: • Mortality should also be included/ added	Comment noted. No action required.
	Histiocytosis UK (Histio UK)	Primary HLH patients are usually managed by immunologists, haematologists and rheumatologists dependent on the nature of their presentation. This falls under highly specialised services. We would anticipate up to 20 patients/yr where this treatment would be considered.	Comment noted. No action required.

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

Department of Health and Social Care