NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

Emapalumab for treating primary haemophagocytic lymphohistiocytosis

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of emapalumab within its marketing authorisation for treating primary haemophagocytic lymphohistiocytosis for national commissioning by NHS England.

Background

Haemophagocytic lymphohistiocytosis (HLH) is characterised by overactivation of the immune system causing severe inflammation throughout the body. 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 interferon gamma (IFNγ) leads to overproduction of pro-inflammatory cytokines and a hyperinflammatory syndrome.

The overactivation of the immune system causes fever, enlargement and damage to the liver and spleen; it also destroys blood-producing cells in the bone marrow. 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 may also be affected, causing impaired muscle coordination, paralysis, blindness and coma. In addition to neurological problems, HLH can cause abnormalities of the heart, kidneys, and other organs and tissues. There is also a risk of developing cancers of blood-forming cells[1] (leukaemia and lymphoma). Without treatment the median survival time ranges from 2 to 6 months; with treatment survival is 55% at 3 years[2].

HLH primarily affects young infants and children, although it can develop for the first time at any age. Primary HLH is the genetic form of the disease, inherited in an autosomal recessive manner. Several specific gene mutations have been identified but not all patients with primary HLH have a recognised genetic mutation.

The incidence of primary HLH is estimated to be 1.2 per million[3] children. Applying the prevalence estimates to the population of England for 2016[4] suggests there are approximately 13 children diagnosed with primary HLH in England each year.

Current treatment for HLH has a two-pronged approach: a short term strategy to control the hyperinflammatory state including steroids, immunosuppressants and chemotherapy, and a long-term strategy aimed at

curative approach by allogeneic hematopoietic stem cell transplantation (HSCT).

The technology

Emapalumab (Gamifant, NovImmune) is a human monoclonal antibody that targets interferon gamma (IFNγ). IFNγ is a cytokine secreted by cells of the immune system to help regulate immune functions. It is administered as an intravenous infusion.

Emapalumab does not currently have a marketing authorisation in the UK for treating primary HLH. It has been studied in clinical trials, in people up to 18 years of age with a confirmed diagnosis of primary HLH.

Intervention(s)	Emapalumab
Population(s)	People with primary haemophagocytic lymphohistiocytosis aged up to 18 years
Comparators	Established clinical management without emapalumab (including ciclosporin, steroids, chemotherapy and allogeneic haematopoietic stem cell transplant)
Outcomes	The outcome measures to be considered include: • overall response • overall survival • time to response • durability of response • use of steroids • long-term complications of HLH • infections • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the

	population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England (2017) Next steps on the five year forward view NHS England (2017) Manual for prescribed specialised services 2017/18 Chapter 113. NHS England (2014) NHS Five year forward view NHS England (2013) 2013/14 NHS standard contract for paediatric oncology E04/S/a NHS England (2013) 2013/14 NHS standard contract

	paediatric medicine: haematology E03/S/f Children, Young People and Maternity Services - archived Department of Health and Social Care (2016) NHS outcomes framework 2016 to 2017

Questions for consultation

How many people have HLH in England, and how many would be offered emapalumab therapy?

How would emapalumab be expected to be used in clinical practice?

- At what point in the treatment pathway would it be considered?
- Would it be used alongside current treatments, or would it replace them?
- Would treatment be expected to continue life-long?

Have all relevant comparators for emapalumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for primary haemophagocytic lymphohistiocytosis?

- In what circumstances is HSCT considered? Would emapalumab be considered as an alternative to HSCT, and/or would it affect the decision of whether or when to consider HSCT?

In what setting is HLH managed in UK clinical practice? Is there a highly specialised service?

Is the population defined appropriately?

How many people would be expected to be considered for emapalumab treatment in clinical practice in England?

Are the outcomes listed appropriate?

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?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eteplirsen will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

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)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is 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.

References

1) U.S. National Library of Medicine – Familial hemophagocytic lymphohistiocytosis https://ghr.nlm.nih.gov/condition/familial-hemophagocytic-lymphohistiocytosis Accessed May 2018

2) Henter J et al. (2002) Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation http://www.bloodjournal.org/content/bloodjournal/100/7/2367.full.pdf?sso%e2%80%90checked=true&sso-checked=true Accessed June 2018

3) Webb D (2010) Histiocytoses http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854-chapter-220407?rskey=Wsrt5W&result=1 Accessed May 2018

4) Population of England (2016) https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates Accessed May 2018