NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

L-glutamine for preventing painful crises in sickle cell disease in people aged 5 years and over

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of L-glutamine within its marketing authorisation for preventing painful crises in sickle cell disease in people aged 5 years and over.

Background

Sickle cell disease is the name given to a group of lifelong inherited conditions that affect haemoglobin. People who have sickle cell disease inherit two abnormal haemoglobin genes, one from each parent. In all forms of sickle cell disease, at least one of the two abnormal genes causes a person's body to produce abnormal haemoglobin, known as haemoglobin S. The condition causes red blood cells to become rigid and misshapen, to resemble a crescent (or sickle)[1]. The most common and often severe type of sickle cell disease occurs when a person acquires 2 haemoglobin S genes (haemoglobin SS). Beta thalassaemia is a blood disorder that reduces the production of healthy red blood cells and haemoglobin in the body. Beta sickle thalassaemia is caused when a person has a sickle mutation in one haemoglobin gene, in addition to the thalassaemia mutation in the other gene (either the 0 or positive mutation). Depending on the beta thalassaemia mutation, people will have either a reduced amount of normal haemoglobin (sickle beta plus thalassaemia) or the more severe form of disease, where they have no normal haemoglobin (sickle beta zero thalassaemia [β0]).

Sickle-shaped red blood cells do not flow easily through the blood vessels and can cause blockages. This may lead to insufficient oxygen being delivered to tissues, causing ischaemic injuries and excruciating pain (known as acute sickle cell crises). Other acute and chronic complications including organ damage, an increased risk of stroke and acute chest syndrome[1]. In people with Sβ thalassaemia there is also a reduction or an absence of mature red blood cells, which can lead to additional symptoms such as anaemia and repeated infections.

It is estimated that there are 14,000 people with sickle cell disease in England[2]. The prevalence of sickle cell disease varies considerably across different ethnic communities, mainly affecting people of African or African-Caribbean origin, although the sickle gene is found in all ethnic groups[3]. The prevalence of the disease is increasing because of immigration into the UK[4]. Sickle cell disease causes significant morbidity and mortality.

Sickle cell disease usually requires lifelong treatment. Management in England focuses on reducing the chances of experiencing a sickle cell crisis by avoiding dehydration, sudden changes in temperature and infection. Sickle cell crises may be extremely painful and will often require emergency admission to hospital and pain management with paracetamol, non-steroidal anti-inflammatory drugs and opiates appropriate to the age and severity of symptoms. Hydroxycarbamide can also be used for the production of foetal haemoglobin, which improves blood cell hydration, and to prevent both acute chest syndrome (caused by reduced blood flow in the lungs) and acute painful crises in people with recurrent painful crises. Allogenic stem cell transplants may be considered in children who have severe disease which does not respond to hydroxycarbamide.

The technology

L-glutamine (Xyndari) is an amino acid that increases the amount of free glutamine circulating in the blood. Glutamine is taken up by the sickle cells and used to generate anti-oxidant molecules as a product of glutamine degradation. Antioxidants neutralise the oxidative stress in sickle red blood cells, allowing them to regain the flexibility needed to travel through blood vessels and capillaries. It is administered orally.

L-glutamine does not currently have marketing authorisation in the UK for any indication. It has been compared with placebo in a clinical trial of people with sickle cell disease or sickle βo-thalassemia aged 5 years and over.

Intervention(s)	L-glutamine
Population(s)	People with sickle cell anaemia or Sickle βo-thalassaemia aged 5 years and over
Comparators	Established clinical management without L-glutamine

Outcomes	The outcome measures to be considered include:
	• mortality
	• number and severity of sickle cell crises including:
	  ○ number and duration of hospitalisations
	  ○ changes to haematological parameters (haemoglobin levels)
	  ○ changes to blood pressure (systolic and diastolic)
	• non-fatal stroke
	• adverse effects of treatment
	• health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Medical Technologies guidance:** Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease (MTG28). March 2016 **Related Guidelines:** Sickle cell disease: managing acute painful episodes in hospital (2012) NICE clinical guideline 143 **Related Quality Standards:** Sickle cell disease (2014) NICE quality standard 58 **Related NICE Pathways:** Sickle cell disease: acute painful episode (2012, updated 2018) NICE pathway
Related National Policy	NHS Commissioning Board Clinical Commissioning Policy Statement: Siklos In Sickle Cell Anaemia 2012 NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1 and 2 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for L-glutamine been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for preventing painful crises in sickle cell disease in people aged 5 years and over? Are the same treatments used in both adults and children?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom L-glutamine is expected to be more clinically effective and cost effective 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 L-glutamine 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 Committee to identify and consider such impacts.

Do you consider L-glutamine 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)?

Do you consider that the use of L-glutamine can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's

Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Source: Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database of Systematic Reviews 2017, Issue 4 (Accessed November 2018)
2. Elizabeth Dormandy, John James, Baba Inusa, David Rees; How many people have sickle cell disease in the UK?, *Journal of Public Health*, Volume 40, Issue 3, 1 September 2018, Pages e291–e295
3. Clinical Knowledge (2016) Sickle cell disease: prevalence (Accessed November 2018)
4. NHS sickle cell and thalassaemia (SCT) screening programme (Accessed November 2018)