

**NIHR Innovation Observatory
Evidence Briefing: JUNE 2018****L-glutamine for sickle cell disease**

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LAY SUMMARY

Sickle cell disease (SCD) is an inherited blood disorder characterized by the production of an altered form of haemoglobin in red blood cells. In sickle cell disease, haemoglobin polymerizes and becomes fibrous, causing red blood cells to become rigid and change form so that they appear 'sickle-shaped' instead of soft and rounded. Patients with sickle cell disease suffer from debilitating episodes of sickle cell crises, which occur when the rigid, adhesive and inflexible red blood cells block other blood vessels. Sickle cell crises cause excruciating pain as a result of insufficient oxygen being delivered to tissues, referred to as tissue ischemia, and inflammation. These events may lead to a variety of other adverse outcomes that require hospitalization.

The amino acid L-glutamine has been developed as an oral powder formulation to reduce the acute complication of sickle cell disease. It is thought L-glutamine works by reducing cell inflammation and promote the cellular uptake of oxygen. If licensed, L-glutamine oral powder may offer an additional therapy option for those with sickle cell disease who currently have few effective therapies available.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Sickle cell disease (≥ 5 years of age)

TECHNOLOGY

DESCRIPTION

L-glutamine oral powder (Xyndari) is an amino acid indicated to reduce the acute complications of sickle cell disease (SCD). The mechanism of action of the amino acid L-glutamine in treating SCD is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic haemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, nicotinamide adenine dinucleotide (NAD⁺) and its reduced form, nicotinamide adenine dinucleotide hydride (NADH), are involved in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.¹

In the phase III clinical trial (NCT01179217), eligible patients received 0.3 g/kg of L-glutamine administered twice a day orally for 48 weeks. Dosing was in increments of 5 grams based on weight, with the upper limit for daily dose set at 30 grams. The powder can be mixed with water or most non-heated beverages other than alcohol, or can be mixed with most non-heated foods such as yogurt, applesauce, or cereal for administration. Mixing L-glutamine with soda or highly acidic juices (such as grapefruit juice or lemonade) is not recommended.² Common adverse effects ($\geq 1/10$) of L-glutamine oral powder include constipation, nausea, headache, abdominal pain, cough, pain in the extremities, back pain and chest pain (non-cardiac).³

L-glutamine oral powder does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

While management of SCD has improved in recent decades, progress in treatment development has been slow. Challenges include the multi-faceted nature of SCD, as well as difficulty in defining biochemical endpoints and targets of clinical benefit in clinical trials. L-glutamine for SCD is only the second United States Food and Drug Administration (FDA) approved treatment for SCD and the first since approved in twenty years.^{4,5} If licensed in the EU/UK, L-glutamine oral powder will offer an additional treatment option for those with SCD who currently have few effective therapies available.

DEVELOPER

Emmaus Life Sciences, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

L-glutamine oral powder is a designated orphan drug in the EU/USA for SCD.⁶

PATIENT GROUP

BACKGROUND

SCD refers to a group of inherited blood disorder characterized by the production of an altered form of haemoglobin which polymerizes and becomes fibrous, causing red blood cells (RBCs) to become rigid and change form so that they appear sickle shaped instead of soft and rounded.⁸ People who have SCD inherit two abnormal haemoglobin genes, one from each parent. In all forms of SCD, at least one of the two abnormal genes causes a person's body to produce abnormal haemoglobin, known as haemoglobin S. When a person acquires two haemoglobin S genes, known as haemoglobin SS, the disease is referred to as sickle cell anaemia. This is the most common and often most severe type of SCD. Haemoglobin SC disease and haemoglobin S β thalassaemia are two other common forms of SCD.⁷

SCD occurs with increasing frequency among those whose ancestors are from regions including Sub-Saharan Africa, South America, the Caribbean, Central America, the Middle East, India and Mediterranean regions such as Turkey, Greece and Italy.⁶ Patients with SCD suffer from debilitating episodes of sickle cell crises, which occur when the rigid, adhesive and inflexible RBCs occlude blood vessels. Sickle cell crises cause excruciating pain as a result of insufficient oxygen being delivered to tissue. These events may lead to a variety of other adverse outcomes such as acute chest syndrome that requires hospitalization.⁸

People born with SCD may experience problems from early childhood, although many children have few symptoms and lead relatively normal lives. Symptoms of SCD include: sickle cell crises, an increased risk of serious infections, and anaemia. Some also experience other complications such as delayed growth, strokes, and problems of the lung. The long-term effects of SCD often begin to emerge during the teenage years and this may be a time of increased episodes of sickle cell crisis. This can have a major impact on education, career, future employment prospects, and social relationships.¹⁴

CLINICAL NEED and BURDEN OF DISEASE

SCD is estimated to affect one in every 2,000 live births in England.⁹ SCD is the most common inherited condition in England, it is estimated that 350 babies are born in England each year with SCD and a further 9,500 babies are found to be carriers of the disease.^{10,11} It is estimated that there are more than 12,500 people with sickle cell disease in England, and roughly 240,000 carriers.¹⁰

A study on trends in hospital admissions for SCD in England 2001-2002 to 2009-2010 showed that the overall admission rate per 100,000 had risen from 21.2 per 100,000 in 2001-2002 to 33.5 per 100,000 in 2009-2010. This rise in admission rates has occurred in every age and sex group with the exception of women aged 30–39 years, whose admission rate per 100,000 population declined from 52.4 to 45.3 over the time period.¹² In England in 2016-17, there were 29,031 finished consultant episodes (FCEs) for sickle cell disorder (ICD-10: D57) resulting in 24,586 admissions and 44, 865 bed days.¹³

Data on survival rates for people with sickle cell disease in the UK are not available as of 2016, however, life expectancy has improved considerably over the last decades due to advances in the management of infections and other complications in childhood, new interventions, active health maintenance for adults, and counselling.¹⁴

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Sickle cell disease: managing acute painful episodes in hospital (CG143). June 2012.
- NICE quality standard. Sickle cell disease (QS58). April 2014.
- NICE medical technologies guidance. Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease (MTG28). March 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Guidance: Sickle cell disease in children: standards for clinical care. October 2010.
- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy. B08/S/a.
- NHS England. 2016/17 NHS public health functions agreement: Service specification No. 18 NHS sickle cell and thalassaemia screening programme. February 2016
- NHS England. Improving Value for Patients from Specialised Care CQUIN Schemes for Prescribed Specialised Services for April 2016 to March 2017. Volume II - The Schemes. March 2016.
- NHS England. Revised Specialised Commissioning CQUINs 2017-18 / 2018-19. September 2016.

OTHER GUIDANCE

- NHS Scotland. Management guidelines for adult patients with sickle cell disease and thalassaemia. 2017.¹⁵
- Imperial College Healthcare NHS. Paediatric Sickle Cell Disease. 2015.¹⁶
- King's College Hospital NHS. Guidelines for the Immediate Management of Paediatric Patients with Sickle Cell Disease (SCD) and Acute Neurological Symptoms. 2014.¹⁷
- King's College Hospital NHS. Guidelines on the Management of a Child with Sickle Cell Disease and low Haemoglobin. 2013.¹⁸

CURRENT TREATMENT OPTIONS

Stem cell or bone marrow transplants are the only cure for SCD, but they are not often undertaken due to significant risks involved. This includes graft versus host disease, which is a life-threatening problem where the transplanted cells begin to attack other cells in the body. To improve transplant success, donated stem cells need to carry a special genetic marker that is identical or very similar to that of the person receiving the transplant. Stem cell transplants are generally only considered in children with SCD who have severe symptoms that have not responded to other treatments, and when the long-term benefits of a transplant are thought to outweigh the possible risks.^{19,20}

The main treatments of SCD involve the prevention and management of painful episodes known as sickle cell crisis. To reduce the chance of sickle cell crisis, those with SCD may need to avoid both dehydration and sudden changes in both body and external temperature. For the treatment of sickle cell crisis, over-the-counter pain killers can be used to relieve the pain, in addition to drinking plenty of fluids and using warm towels or heat pads on the affected part of the body. Hydroxycarbamide (hydroxyurea) may be recommended if the patient continues to experience pain episodes. Hydroxycarbamide is a medication that is usually taken orally. It can lower the amount of other blood

cells, such as white blood cells and platelets (clotting cells). Regular blood tests will usually be recommended to monitor a patient’s health.¹⁹

Treatment of anaemia caused by SCD may require dietary supplements such as folic acid. This is particularly notable for those with restricted diet, such as vegetarians or vegans. Anaemia caused by SCD is not the same as the more common iron deficiency anaemia. Patients should not take iron supplements without seeking medical advice. If anaemia is particularly severe or persistent, treatment with blood transfusions or hydroxycarbamide may be necessary. NICE recommends the use of Spectra Optia for automated red blood cell exchange in patients with SCD who require regular transfusion.²¹

EFFICACY and SAFETY

Trial	NCT01179217 ; L-glutamine vs maltodextrin (placebo); phase III
Sponsor	Emmaus Medical, Inc.
Status	Published
Source of Information	Publications ^{6,22} Trial registry ²
Location	USA
Design	Randomised, double-blind, placebo-controlled, parallel-group
Participants	n=230; aged ≥5 years; diagnosed with sickle cell anaemia or sickle β°-thalassemia (documented by haemoglobin electrophoresis); at least two documented episodes of sickle cell crises within 12 months of the screening visit
Schedule	Randomised to receive 0.3 g/kg of L-glutamine administered twice a day orally for 48 weeks vs placebo. Dosing was in increments of 5 grams based on weight, with the upper limit for daily dose set at 30 grams.
Follow-up	From baseline up to 48 weeks.
Primary Outcomes	<ul style="list-style-type: none"> The number of occurrences of sickle cell crises [Time Frame: 48 weeks] The number of occurrences of protocol-defined sickle cell crises that occur from Week 0 to Week 48 will be used to evaluate the efficacy of oral L-glutamine as a treatment for sickle cell anaemia and beta-0 thalassemia.
Secondary Outcomes	<ul style="list-style-type: none"> The number of hospitalizations for sickle cell pain [Time Frame: 48 weeks] The number of hospitalizations that occur from Week 0 to Week 48, will be used to evaluate the efficacy of oral L-glutamine as a treatment for sickle cell anaemia and beta-0 thalassemia. The number of emergency room/medical facility visits for sickle cell pain [Time Frame: 48 weeks] The number of emergency room visits or medical facility visits that occur from Week 0 to Week 48, will be used to evaluate the efficacy of oral L-glutamine as a treatment for sickle cell anaemia and beta-0 thalassemia. The effect of oral -L-glutamine on haemoglobin parameters [Time Frame: Baseline, Week 4, 24 and 48] To assess the effect of oral L-glutamine on haematological parameters (haemoglobin), Change from Baseline will be reported at Weeks 4, 24 and 48.

	<ul style="list-style-type: none"> • The effect of oral L-glutamine on vital signs [Time Frame: Baseline, Week 4, 24, and 48] To assess the effect of oral L-glutamine on Vital signs (systolic and diastolic blood pressure). Change from Baseline will be reported at Weeks 4, 24, and 48. • The effect of oral L-glutamine on haematological parameters [Time Frame: Baseline, Week 4, 24 and 48] To assess the effect of oral L-glutamine on haematological parameters (haematocrit), Change from Baseline will be reported at Weeks 4, 24 and 48. • The effect of oral L-glutamine on haematological parameters [Time Frame: Baseline, Week 4, 24 and 48] To assess the effect of oral L-glutamine on haematological parameters (reticulocyte count), Change from Baseline will be reported at Weeks 4, 24 and 48. • The effect of oral L-glutamine on vital signs [Time Frame: Baseline, Week 4, Week 24 and Week 48] To assess the effect of oral L-glutamine on Vital signs (pulse rate). Change from Baseline will be reported at Weeks 4, 24, and 48. • Effect of oral L-glutamine on vital signs [Time Frame: Baseline, Week 4, Week 24 and Week 48] To assess the effect of oral L-glutamine on Vital signs (temperature). Change from Baseline will be reported at Weeks 4, 24, and 48. • The effect of oral L-glutamine on vital signs [Time Frame: Baseline, Week 4, Week 24 and Week 48] To assess the effect of oral L-glutamine on Vital signs (respiration). Change from Baseline will be reported at Weeks 4, 24, and 48.
Key Results	Patients who were treated with L-glutamine oral powder over a 48-week period demonstrated a 25% decrease in the median frequency of sickle cell crises and 33% decrease in the median number of hospitalizations, as compared to placebo. Based on an analysis, utilizing pre-specified statistical methods, the difference between groups was statistically significant; $p=0.0052$ and $p=0.0045$, respectively. Other clinically relevant endpoints showed similar results such as a 66% lower incidence of acute chest syndrome ($p=0.0028$), 41% less cumulative days in hospital ($p=0.022$), and 56% delay in onset of the first sickle cell crisis ($p=0.0152$). The safety data collected demonstrated a safety profile similar to that of placebo. ⁶
Adverse effects (AEs)	Common adverse effects ($\geq 1/10$) of L-glutamine oral powder include constipation, nausea, headache, abdominal pain, cough, pain in the extremities, back pain and chest pain (non-cardiac). ^{6,22}
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of L-glutamine oral powder is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs
- Other: *uncertain unit cost*
- None identified

OTHER ISSUES

- None identified

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