NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

CTX001 for treating transfusion-dependent beta-thalassaemia

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of CTX001 within its marketing authorisation for treating transfusion-dependent beta-thalassaemia

Background

Thalassaemia is a group of hereditary blood disorders caused by a genetic mutation of the haemoglobin subunit beta (HBB) gene. The condition is characterised by reduced production of healthy red blood cells and haemoglobin in the body, which is used by red blood cells to carry oxygen around the body. There are two basic groups of thalassaemia: alpha-thalassaemia and beta-thalassaemia. Beta-thalassaemia comprises of several phenotypes with different severity. Beta-thalassaemia major is the most severe type which is transfusion-dependent requiring regular red blood cell (RBC) transfusions. However, people with severe forms of thalassaemia intermedia may also require regular RBC transfusions.

Thalassaemia causes varying degrees of anaemia, leading to symptoms such as tiredness, weakness, shortness of breath and pale skin caused by the lack of haemoglobin. In transfusion-dependent beta-thalassaemia, haemoglobin production is reduced to such a low level that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy. The most severe cases can lead to heart failure or liver complications.

The National Haemoglobinopathy Registry reports that in 2020/21 approximately 1000 people were registered with beta-thalassaemia major and approximately 260 with beta-thalassaemia intermedia.[1] The prevalence of thalassaemia varies considerably across different ethnic communities, mainly affecting people of Mediterranean, South Asian, South East Asian and Middle Eastern family origin. In the UK, the highest prevalence of thalassaemia is seen in ethnic minority populations, the largest groups being people of Pakistani, Indian and Bangladeshi family origin.

Transfusion dependent beta-thalassaemia usually requires lifelong treatment with blood transfusions and medication. The frequency of blood transfusions can vary but is typically every 3 to 4 weeks, and repeated transfusions are associated with an increased risk of bloodborne infections and graft versus host disease. Treatment with transfusions can cause too much iron to build up in the body and lead to complications including liver cirrhosis, endocrine complications such as diabetes, sterility, and heart failure. Therefore, chelation therapy (medication to remove excess iron from the body) is also a key component in managing transfusion-dependent beta thalassaemia. Chelation therapy itself is associated with adverse events including kidney failure, liver and heart toxicity. The only potentially curative intervention is a haematopoietic stem cell transplant, but these transplants carry significant risks and are only considered for people under the age of 18 years who have a matching donor (approximately 30% of people with transfusion-dependent beta-thalassaemia[2]).

The technology

Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) (brand name unknown, Vertex Pharmaceuticals Inc and CRISPR Therapeutics).

CTX001 does not currently have a marketing authorisation in the UK for treating transfusion-dependent beta-thalassaemia. It has been studied in 2 single arm clinical trials of people aged 12 to 35 years with transfusion-dependent beta-thalassemia who were eligible for autologous stem cell transplant and a long-term follow-up study of patients 2+ years with either transfusion-dependent beta-thalassemia or sickle cell disease who were eligible for autologous stem cell transplant.

Intervention(s)	Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001)
Population(s)	Transfusion-dependent beta-thalassaemia
Comparators	Established clinical management of beta-thalassaemia without CTX001 including: • blood transfusions and chelating agents • allogenic stem cell transplants • best supportive care.
Outcomes	The outcome measures to be considered include: • reduction in transfusions • changes to haematological parameters (haemoglobin levels) • proportion with and time to engraftment • new or worsening hematologic disorders • mortality • 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	**Related technology appraisals in development:** Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. NICE technology appraisal guidance [ID968] Publication date to be confirmed Luspatercept for treating anaemia in non-transfusion dependent beta-thalassaemia. NICE technology appraisal guidance [ID3870] Publication date to be confirmed **Terminated technology appraisals:** Luspatercept for treating beta-thalassaemia. NICE technology appraisal guidance [TA843] November 2022
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2017) NHS Medicines for Children's Policy NHS England (ongoing) Specialised haemoglobinopathy services - Thalassemia – Haemoglobinopathies Coordinating Centres (HCCs) NHS England (2018) NHS manual for prescribed specialist services (2018/2019) Chapter 114 Specialist haemoglobinopathy services (adults and children) Public Health England (2018) Service specification NHS Sickle cell and Thalassaemia Screening Programme (2018-2019) NHS England (2016) Specialised Services clinical commissioning policies and service specification - Wave 13 NHS England (2016) Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias NHS England (2013) 2013/14 NHS standard contract for specialised services for haemoglobinopathy care (all ages)

Questions for consultation

How do you define transfusion-dependence in clinical practice?

Where do you consider CTX001 will fit into the existing care pathway for transfusion-dependent beta-thalassaemia? Is the current comparator accurate? Should hematopoietic stem cell transplant be considered a comparator?

Would CTX001 be a candidate for managed access?

Do you consider that the use of CTX001 can result in any potential 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 committee to take account of these benefits.

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 CTX001 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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. The National Haemoglobinopathy Register. (2021) Annual data report 2020/21. https://nhr.mdsas.com/wp-content/uploads/2022/03/NHR_DataReport2021.pdf. Accessed November 2022.

2. Angelucci E, Matthes-Martin S, Baronciani D et al. (2014) Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica 99: 811-20.