NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of exagamglogene autotemcel 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 or absence 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 main forms 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 (for example severe beta plus globin mutations or haemoglobin E beta thalassaemia) may also require regular RBC transfusions and, therefore, could also be considered 'transfusion-dependent'.

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, skeletal and endocrine 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 from anaemia, liver complications from excess iron due to regular transfusions, and pulmonary hypertension or other complications related to thrombotic events.

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 requires lifelong treatment with blood transfusions and medication. The frequency of blood transfusions can vary but is typically every 2 to 4 weeks, and repeated transfusions are associated with increased risks of allo-immunisation, infections, graft versus host disease, or other serious hazard of transfusion events. In addition, treatment with transfusions causes too much iron to build up in the body. At a moderate iron overload, this can lead to endocrine complications such as diabetes, hypothyroidism, hypogonadotropic hypogonadism, sterility, heart dysfunction, and severe and chronic bone and join

paint. With more severe and prolonged iron overload, heart failure and cardia arrythmias can lead to ill health and death and late effects such as liver cirrhosis, portal hypertension and liver failure. Therefore, chelation therapy (medication to remove excess iron from the body) is also a key component in managing transfusion-dependent beta thalassaemia. 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 10 to 30% of people with transfusion-dependent beta-thalassaemia[2]).

The technology

Exagamglogene autotemcel (brand name unknown, Vertex Pharmaceuticals Inc and CRISPR Therapeutics).

Exagamglogene autotemcel 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 (defined as a history of at least 100ml/kg year or 10 units/year of packed RBC transfusion in the prior 2 years) who were eligible for autologous stem cell transplant but did not have a human leukocyte antigen (HLA)-matched related donor 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	Exagamglogene autotemcel
Population	Transfusion-dependent beta-thalassaemia where there is no human leukocyte antigen (HLA)-matched related donor
Subgroups	If the evidence allows the following subgroups will be considered: • people with beta thalassaemia major • people with beta thalassaemia intermedia
Comparators	Established clinical management of beta-thalassaemia without exagamglogene autotemcel including: • blood transfusions and chelating agents • best supportive care.

Outcomes	The outcome measures to be considered include: • reduction in transfusions • changes to haematological parameters (haemoglobin levels) • reduction in the use of iron chelating agents • 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:** Luspatercept for treating anaemia in non-transfusion dependent beta-thalassaemia. NICE technology appraisal guidance [ID3870] Publication date to be confirmed
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 (2023) NHS manual for prescribed specialist services (2023) 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)

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.