NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zynteglo for treating transfusion-dependent beta-thalassaemia

Final scope

Remit/appraisal objective

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

Background

Thalassaemia is the name for a group of inherited blood disorders caused by a genetic mutation of the HBB gene that leads to 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. The most severe forms are known as transfusion-dependent thalassaemia (or thalassaemia major) and the least severe forms as non-transfusion-dependent thalassaemia (thalassaemia minor). Depending on whether one or both alleles of the HBB gene is affected the disease can be categorised into different genotypes. Total absence of the production of beta globin due to a mutation in both alleles of the HBB gene is called beta-zero (β0/β0) genotype. 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 so reduced that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy.

Beta-thalassaemia affects around 1 in 100,000 of the population in England.[1] There are currently 996 people diagnosed with beta-thalassaemia major in the UK according to the National Haemoglobinopathy Registry.[2] The prevalence of thalassaemia varies considerably across different ethnic communities, mainly affecting people of Mediterranean, South Asian, South East Asian, African, Caribbean, South American and Middle Eastern origin. In the UK, transfusion-dependent beta-thalassaemia is almost exclusively seen in ethnic minority populations, the largest groups being Pakistani, Indian and Bangladeshi.[1]

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 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).

The technology

Zynteglo (bluebird bio) is an autologous beta-globin gene therapy that comprises a lentiviral vector which inserts functional copies of a beta globin gene, known as β-A^{T87Q} into CD34+ haematopoietic stem cells, ex vivo. The resulting engineered stem cells are then reintroduced to the patient by intravenous infusion. Before the infusion, myeloablative chemotherapy using busulfan is given.

Zynteglo has a marketing authorisation in the UK. It is indicated for the 'treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β0/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related haematopoietic stem cell transplantation donor is not available'.

Intervention	Zynteglo gene therapy (autologous CD34+ cells encoding βA-T87Q-globin gene)
Population	People aged 12 years and over with transfusion-dependent beta-thalassaemia with a non-β0/β0 genotype, who are eligible for hematopoietic stem cell transplantation but do not have access to a matched related donor
Comparators	Established clinical management of transfusion-dependent beta-thalassaemia, including blood transfusions and chelating agents
Outcomes	The outcome measures to be considered include: • overall survival • symptoms of anaemia • need for transfusion • iron overload complications (e.g. cardiac, liver and endocrine complications) • growth and development (for non-adults) • 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: 'Desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia' (suspended appraisal). NICE technology appraisal guidance [ID350].
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2016) Clinical Commissioning Policy: Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 114 - Specialist haemoglobinopathy services (adults and children) NHS England (2013) 2013/14 NHS standard contract for specialised services for haemoglobinopathy care (all ages) Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4, 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 East Midlands Specialised Commissioning Group (2011) The National Haemoglobinopathies Project: a guide to effectively commissioning high quality sickle cell and thalassaemia services Public Health England (2012, updated 2018) Sickle cell and thalassaemia: screening handbook

References

1. National Haemoglobinopathy Registry Annual Report 2018/19, National Haemoglobinopathy Registry. Accessed July 2019

2. Number of patients by diagnosis, National Haemoglobinopathy Registry. Accessed July 2019