Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Health Technology Appraisal

Luspatercept for treating anaemia in non-transfusion dependent beta-thalassaemia [ID3870]

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of luspatercept within its marketing authorisation for treating anaemia in non-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.[1] There are two basic groups of thalassaemia: alpha-thalassaemia and beta-thalassaemia.[2] 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, usually administered every 2 to 5 weeks.[3]

People with non-transfusion dependent beta-thalassemia do not need lifelong regular transfusions for survival but may have occasional or even frequent transfusions in certain clinical settings and for defined periods of time.[4,5] Non-transfusion dependent beta-thalassemia may include beta-thalassaemia intermedia, beta-thalassemia minor as well as beta-thalassemia with associated haemoglobin (Hb) anomalies such as Haemoglobin E/beta thalassaemia. These types of beta-thalassaemia are characterised based on genetic factors and the severity of symptoms.[4]

The main health problems associated with non-transfusion dependent beta-thalassaemia are ineffective red blood cell production, chronic anaemia and iron overload.[1,5] Symptoms of anaemia include tiredness and general lack of energy, shortness of breath, pounding, fluttering or irregular heartbeats (palpitations) and pale skin caused by the lack of haemoglobin.[1] Blood transfusion may be required to stop anaemia becoming too severe. People with more severe types of beta-thalassemia are at risk of developing a range of health problems caused by too much iron in the body. It is usually a side effect of the regular blood transfusions used to treat anaemia and can cause problems with the heart, liver, and hormone levels if untreated.[1]

The National Haemoglobinopathy Registry reports that in 2019/20 approximately 250 people were registered with beta-thalassaemia intermedia and approximately 120 with Haemoglobin E/beta-thalassaemia in England.[6] 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.[4] 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.[6]

Non-transfusion dependent beta-thalassaemia usually requires lifelong management including treatment with occasional and sometimes frequent blood transfusions and

medicine (chelating agents).[1,7] Chelation therapy, such as desferrioxamine, deferiprone or deferasirox,[3,4] removes excess iron from the body.

The technology

Luspatercept (Reblozyl, Bristol-Myers Squibb), an erythroid maturation agent, is a recombinant engineered protein designed to attach to ligands of transforming growth factor-beta (TGF-beta) and inhibit cell signalling, which is abnormal in beta-thalassemia, thereby enabling the maturation of red blood cells. Luspatercept is administered subcutaneously.

Luspatercept does not currently have a marketing authorisation in the UK for non-transfusion dependent beta-thalassemia. It has been studied in a clinical trial of luspatercept compared with placebo in adults with beta-thalassemia who do not require regular red blood cell transfusions.

Luspatercept has a marketing authorisation in the UK for the treatment of adults with transfusion-dependent anaemia associated with beta-thalassemia and myelodysplastic syndromes.

Intervention(s)	Luspatercept
Population(s)	Adults with anaemia associated with non-transfusion dependent beta-thalassaemia
Comparators	Established clinical management of non-transfusion dependent beta-thalassaemia without luspatercept
Outcomes	The outcome measures to be considered include: • change in anaemia • change in beta-thalassemia related symptoms (for example, fatigue/tiredness and weakness) • reduction in blood transfusions • change in iron levels • reduction in dosing of iron chelation therapy • duration of erythroid response (haemoglobin increase) • overall survival • adverse effects of treatment • health-related quality of life.

Appendix B

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 Technology Appraisals: Appraisals in development (including suspended appraisals) Luspatercept for treating beta-thalassaemia (suspended). NICE Technology Appraisal ID1554. Luspatercept for treating anaemia caused by myelodysplastic syndromes (suspended). NICE Technology Appraisal ID1550. Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia (suspended). NICE Technology Appraisal ID968. Related Quality Standards: Blood transfusion (2016). NICE quality standard 138. Related NICE Pathways: Blood conditions (2021). NICE pathway. Blood transfusion (2016). NICE pathway.
Related National Policy	**NHS England** The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (ongoing) Specialised haemoglobinopathy services - Thalassemia – Haemoglobinopathies Coordinating Centres (HCCs) accessed September 2021 NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 114. Specialist haemoglobinopathy services (adults and children) NHS England (2018) Service specification NHS Sickle cell and Thalassaemia Screening Programme (2018-2019) NHS England (2016) Clinical Commissioning Policy:

	Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 1, 2, 4, 5 **Public Health England** Public Health England (updated 2020) Beta thalassaemia carrier: description in brief Public Health England (2015) Sickle cell and thalassaemia screening: community outreach good practice

Questions for consultation

How is non-transfusion dependent beta-thalassemia defined in clinical practice in England?

Is it expected that use of luspatercept would replace or reduce blood transfusions and iron chelation therapy in clinical practice?

If iron chelation therapy is expected to be reduced or displaced by the use of luspatercept, which medicines are usually used in clinical practice for iron chelation therapy?

Have all relevant comparators for luspatercept been included in the scope? Which treatments are established clinical practice in the NHS for non-transfusion dependent beta-thalassemia?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom luspatercept is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider luspatercept will fit into the existing NICE pathway for Blood Conditions?

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 luspatercept is 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 luspatercept 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 luspatercept 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. NHS conditions (2016). Thalassaemia. https://www.nhs.uk/conditions/thalassaemia/ Accessed September 2021.

2. Porter J, Taher A, Mufarrij A et al. (2012) Emergency management of thalassaemia. Thalassaemia International Federation. https://ukts.org/3d-flip-book/emergency/ Accessed September 2021.

3. Cappellini MD, Farmakis D, Porter J et al. (2021) Guidelines for the management of transfusion dependent thalassaemia (TDT), 4th Edition. Thalassaemia International Federation. https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf Accessed September 2021.

4. Taher A, Musallam K, Cappellini MD. (2017) Guidelines for the management of non transfusion dependent thalassemia (NTDT), 2nd Edition. Thalassaemia International Federation. https://www.thalassemia.org/boduw/wp-content/uploads/2011/09/Guidelines-for-Mgmt-of-NTDT-TIF-2017.pdf Accessed September 2021.

5. Sleiman J, Tarhini A, Bou-Fakhredin R et al. (2018) Non-transfusion dependent thalassemia: an update on complications and management. International Journal of Molecular Science 19:182.

6. The National Haemoglobinopathy Register. (2021) Annual data report 2019/20. https://nhr.mdsas.com/wp-content/uploads/2021/01/2020_12_NHR_AnnualReport201920_Final.pdf Accessed September 2021.

7. UK Thalassemia Society. (2016) Standards of care for the clinical care of children and adults with thalassemia in the UK, 3rd Edition. https://ukts.org/3d-flip-book/standards/ Accessed September 2021.