National Institute for Health and Care Excellence

Single Technology Appraisal

Luspatercept for treating beta-thalassaemia ID1554

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness *Would it be appropriate to refer this topic to NICE for appraisal?*	Celgene	Yes	Thank you for your comment. No further action required.
	UK Thalassaemia Society	The United Kingdom Thalassaemia Society is in agreement that the application for Luspatercept should be referred to NICE for appraisal as this novel therapy will be able to assist a wider range of patients, especially as the anticipated marketing authorisation for Luspatercept will not be defined for β-thalassemia major or intermediate patients but rather it will be determined by transfusion dependence in adults. β-thalassemia can be chronic and severely disabling resulting in a variety of comorbidities associated with repeated blood transfusions and iron overload. Currently, the treatment for thalassaemia consists of regular red cell transfusions ranging from every two to four weeks in addition to a rigorous daily iron chelation regime which is due to the increased levels of iron accumulated from repeated blood transfusions. Iron overload from blood	Thank you for your comment. No further action required.

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		transfusions is one of the biggest contributors in increasing the risks associated with mortality and morbidity observed in thalassaemia. At the moment the only curative treatment is Allo Hamatopoietic Stem Cell transplantation which is only available to patients with an HLA matched related donor. UK British Society for Bone Marrow Transplantation recommends Allo HSCT in patients under 12. This excludes a significant population of the thalassaemia community in the UK. Additionally, Allo HSCT can result in severe treatment related risks such serious infections, graft versus host disease, graft failure, infertility and even death. Luspatercept offers a possibility of a reduction of red cell transfusions. Not only will this reduce hospital visits and risks of infection but also decrease iron burden which can result in cardiac, hepatic and endocrine failure and increase a patient and their families overall quality of life (Porter, 2019). The overall cost to the National Health Service will also decrease due to repeated blood transfusions and comorbidities associated with iron overload.	
	Genetic Alliance UK	Given the prevalence of beta-thalassaemia It would be appropriate that luspatercept is assessed using the single technology appraisal route.	Thank you for your comment. No further action required.
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not,*	Celgene	[redacted]	Thank you for your comment. No further action required.

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please suggest alternative wording	UK Thalassaemia Society	The wording of the remit is misleading. The remit should include “transfusion dependent”, as not all patients with beta thalassaemia require regular blood transfusions. Additionally, the wording should also be clearer in outlining who the target population is targeting ie. Adults The remit should be amended as follows: To appraise the clinical and cost effectiveness of luspatercept within its marketing authorisation for treating transfusion dependent adults with a form of β-thalassemia.	Thank you for your comment. In order to allow flexibility, the remit for the scope has been kept broad to cover the whole anticipated marketing authorisation.
	Genetic Alliance UK	This is the standard wording.	Thank for your comment. No further action required
Timing Issues *What is the relative urgency of this proposed appraisal to the NHS?*	Celgene	Currently there is no licensed option other than supportive care for patients who have beta thalassaemia associated anaemia. Therefore there is an unmet need that luspatercept could fulfil.	Thank you for your comment. NICE aims to publish draft guidance within 6 months of marketing authorisation.
	UK Thalassaemia Society	Studies published to date indicate that Luspatercept increases haemoglobin which in turn reduces the overall frequency of transfusions (Porter, 2019). This not only decreases iron burden and comorbidities but also may result in an overall cost reduction to the NHS for hospital for transfusion visits, iron chelation, inpatient stays and specialist clinics. There may also be a decrease in the demand for blood which will help with the current blood shortage observed by NHSBT.	Thank you for your comment. NICE aims to publish draft guidance within 6 months of marketing authorisation.

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		This novel treatment may also improve the quality of life for patients and their families due to the reduction of hospital visits as patients and their families need to take time off education and work to attend treatment days, clinics and examinations. A reduction in transfusions will give patients a chance of experiencing some form of normalcy as their non transfusion peers have; and may even give them the opportunity to travel for for extended periods of time- which at present they cannot do. **This is a positive outcome for all parties involved and as a result we feel that access to this treatment should be prioritised as a matter of urgency.**	
	Genetic Alliance UK	As treatment options for beta thalassaemia are limited to blood transfusions and iron chelating agents, which can lead to viral infections and other complications it is a matter of urgency that this technology is assessed as soon as possible.	Thank you for your comment. NICE aims to publish draft guidance within 6 months of marketing authorisation.

Comment 2: the draft scope

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Background information *Consider the accuracy and completeness of this information.*	Celgene	A subset of persons with the phenotype beta-thalassaemia intermedia can also be transfusion dependent	Thank you for your comment. The background section of the scope is designed to give a brief overview and is not able to comprehensively detail all aspects of a disease area. The evidence on

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			whether beta-thalassaemia intermedia is transfusion dependent is mixed in the literature. However, the background section of the scope has been updated to make this clearer.
	UK Thalassaemia Society	The background information provided gives a good description of thalassaemia but does not mention what the criteria is for determining transfusion dependence. It is also not specific enough in identifying transfusion dependent patients as, in addition, to some beta thalassaemia major and intermediate patients requiring life long blood transfusions, some patients with Haemoglobin E disease also require red cell transfusions. Secondly, the figures quoted for the numbers of beta thalassaemia patients in the UK needs updating. As of May 2019, the figures for the number of patients living with any of the thalassaemia syndromes have been updated on the National Haemoglobinopathy Register. There are currently 1,380 people diagnosed with β-thalassemia in the UK of which 996 have beta thalassaemia major, 246 have beta thalassaemia intermedia and 138 have beta thalassaemia/Hb E disease. Thirdly, the background information other parts of the world where thalassaemia is prevalent such as South America, the Caribbean and Africa.	Thank you for your comment. The background section of the scope is designed to give a brief overview and is not able to comprehensively detail all aspects of a disease area. However, the background section has been updated to include the most updated figures from the National Haemoglobinopathy Register (June 2019), and to give more details about transfusions dependence.

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		The background information also does not mention the risks associated with having repeated transfusions in beta thalassaemia such as the increased risk of developing reactions due to alloimmunisation (allergic, haemolytic), bloodborne infections, graft versus host disease and the risk of developing transfusion related acute lung injury (Azarkeivan et al., 2011). Furthermore,the background information does not mention the risks involved with repeatedly using iron chelation medication such as kidney failure, ophthalmic and audiological deterioration, liver and heart toxicity, bone pain etc. Lastly, the background information should also mention the number of patients who would be eligible in accessing this new treatment. The information provided states that the new treatment may be available for adults but it is not clear what the age ranges would be or whether there would be a cut off point after a certain age.	
The technology/ intervention *Is the description of the technology or technologies accurate?*	Celgene	Yes	Thank you for your comment. No further action required
	UK Thalassaemia Society	The description of the technology states it is “a recombinant engineered protein that is designed to attach to certain protein that inhibit the maturation of blood cells.” This should be more detailed and should be more specific with regards to the mechanisms of which blood cell protein it inhibits.	Thank you for your comment. The intervention section has been updated to clarify that TGF-beta proteins are inhibited.

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Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Celgene	Yes	Thank you for your comment. No further action required.
	UK Thalassaemia Society	The scopes states the target population intends to be avaible for “adults” and this is appropriate, however, as there is no efficacy or safety data available outside the study’s inclusion and exclusion criteria, the population should be limited to the anticipated licensed indicated until more data becomes available.	Thank you for your comment. No further action required.
Comparators *Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as ‘best alternative care’?*	Celgene	Yes	Thank you for your comment. No further action required.
	UK Thalassaemia Society	The comparators listed for transfusion dependent thalassaemia adults (i.e blood transfusions and chelation therapy) are standard treatments used by patients who do not have access to an allo HSCT.	Thank you for your comment. No further action required.
Outcomes *Will these outcome measures capture the most important health related*	Celgene	The change in number of red blood cell units transfused is also an important outcome to consider along with the frequency.	Thank you for your comment. The outcomes have been updated to include change in red blood cell transfusion units.

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benefits (and harms) of the technology?	UK Thalassaemia Society	The outcomes should also include the cost reduction to the NHS with reduced blood transfusions and the reduction in demand of blood stocks on placed on the NHSBT.	Thank you for your comment. The outcomes measures are health related benefits and harms. However, costs are accounted for in the cost-effectiveness analysis.
Economic analysis *Comments on aspects such as the appropriate time horizon.*	Celgene	As per reference case	Thank you for your comment. No further action needed.
	UK Thalassaemia Society	Research published by Karnon et al (1999) estimates the lifetime costs of a beta thalassaemia patient to be approximately 803,002 pounds sterling where as research published by Weidlich et al (2016) based on 2013 costs, estimates lifetime costs without any comorbidities to be around 483,545 pounds sterling. Based on the disparity across both studies and the impact of UK's depature from the European Union, it is difficult to comment what the potential costs of treatment for treatment of transfusion dependent beta thalassaemia patients will be. The data shows a reduction in transfusion volume and frequency, which will reduce the demand place on NHSBT and the NHS over time.	Thank you for your comment. No further action needed.
Equality and Diversity	Celgene	If transfusion burden is defined it may lead to inequity for patients with whose transfusion burden is considered outside of this definition.	Thank you for your comment. Equalities considerations will be addressed in the Equalities Impact

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			Assessment form in detail.
	UK Thalassaemia Society	NONE	Thank you for your comment. No further action required
	Genetic Alliance UK	The condition is particularly prevalent in the UK among those from south Asian, Mediterranean and Middle-Eastern backgrounds.	Thank you for your comment. Equalities considerations will be addressed in the Equalities Impact Assessment form in detail.
Other considerations	UK Thalassaemia Society	NONE	Thank you for your comment. No further action required.
Innovation *Do you consider the technology 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*	Celgene	Current treatment options for beta-thalassaemia are limited to blood transfusions and iron chelating agents which remain the mainstay of treatment. However, these treatments may lead to complications such as viral infections, iron overload and other complications. Luspatercept has the potential to provide benefit in a variety of conditions in which ineffective erythropoiesis contributes significantly to anaemia and overall disease morbidity, including beta-thalassaemia. In beta-thalassemia, luspatercept is a novel approach for treating anaemia, with potential to improve many patients' lives by reducing or eliminating the need for frequent and lifelong blood transfusions. Luspatercept works by targeting specific TGF-beta proteins involved in late-stage RBC maturation, stimulating RBC production and thereby preventing	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.

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management of the condition)? *Do you consider that the use of the technology 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.*		anaemia. This mechanism of action has the potential to be transformative for patients with serious RBC disorders by significantly reducing or eliminating the need for frequent and lifelong blood transfusions.	
	UK Thalassaemia Society	Yes, the UKTS considers the technology to be novel. The trial data published on the mechanisms of luspartercept could provide a possible reduction in blood transfusion requirements and associated iron overload.	Thank you for your comment. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology.
	Genetic Alliance UK	Clinical trials of luspatercept have shown promising results in terms of a reduction in transfusion burden and the healing of ulcers and an overall reduction in disease burden. It represents a step-change in the management of the condition.	Thank for your comment. No further action required.
Questions for consultation *Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely*	Celgene	In the current treatment pathway, luspatercept would be used once patients are receiving red blood cell transfusions. Studies are underway assessing luspatercept in people who are non-transfusion dependant (receives transfusions but not regularly)	Thank you for your comment. The technology will be appraised within its marketing authorisation. No further action required.
	UK Thalassaemia Society	**How is transfusion dependent thalassaemia defined in practice?** Transfusion Dependent in Thlassaemia is defined as receiving 8 or more red blood cell transfusions per year (Cappellini et al., 2014).	Thank you for your comment. No further action required.

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to result in changes to the planned time lines).		**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?** Yes, The impact of fewer transfusions and time off education and work may decrease anxiety levels with taking time off. Additionally, the reduced transfusions and iron burden, may reduce symptoms of depression. The increased haemoglobin levels will also allow patients to feel better for longer and the increased transfusion free period will allow patients to participate in activities that are usually limited due to blood transfusion requirements. Thus, increasing the overall quality of life. Reduced transfusions and reduced iron loading will also increase quality of life for parents and families of beta thalassaemia patients.	Thank you for your comment. we encourage companies to submit all relevant and available evidence for consideration.
Additional comments on the draft scope	Celgene	Celgene are aware that there is a planned review of the criteria for HST appraisals in Summer 2019. We believe that luspatercept for beta-thalassaemia would ideally be considered via the HST route. The current criteria for selection via the HST route are as follows: • The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS; • The target patient group is distinct for clinical reasons; • The condition is chronic and severely disabling;	Thank you for your comment. Following consultation, it was agreed that the appropriate route for luspatercept was as a single technology appraisal. This decision was based on the expected use of

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		• The technology is expected to be used exclusively in the context of a highly specialised service; • The technology is likely to have a very high acquisition cost; • The technology has the potential for life long use; • The need for national commissioning of the technology is significant. The only criteria that luspatercept is unlikely to meet at the current time is 'The technology is expected to be used exclusively in the context of a highly specialised service' as a second indication for anaemia caused by myelodysplastic syndromes is expected. [redacted]We would welcome a discussion with NICE over the potential to review luspatercept for beta-thalassemia under the HST program.	luspatercept in multiple centres in the NHS due to the population size and that luspatercept is not expected to be used exclusively in the context of a highly specialised service.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope