National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Luspatercept for treating anaemia caused by myelodysplastic syndromes ID1550

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	British Society for Haematology and Royal College of Pathologists	Yes. There is a paucity of treatment options for 'lower' risk MDS.	Comment noted. No action required.
	Celgene	Yes	Comment noted. No action required.
Wording	British Society for Haematology and Royal College of Pathologists	Reasonably	Comment noted. No action required.
	Celgene	Yes	Comment noted. No action required.
Timing Issues	British Society for Haematology and Royal College of Pathologists	Not urgent	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Celgene	There are currently no licensed treatment options for anaemia in patients intolerant/ineligible or refractory to erythropoiesis-stimulating agents (ESAs) in very low, low or intermediate MDS	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Society for Haematology and Royal College of Pathologists	The background is average. This could be improved. For instance, anaemia is not a symptom, what are the intravenous infusions that are referred to? It would be helpful to have a fuller discussion regarding best supportive care (BSC) particularly the challenges and hazards of transfusion as at the end of the day is the main comparator.	Comment noted. The background section has been updated to include complications of red blood cell transfusions.
	Celgene	The IPSS-R scoring also considers cytogenetics factors.	Comment noted, cytogenic factors have been listed in the background section.
The technology/ intervention	British Society for Haematology and Royal College of Pathologists	See comments on population	Comment noted.
	Celgene	The brand name for luspatercept is REBLOZYL. The ongoing PACE-MDS, phase II study is assessing Luspatercept for the treatment of anaemia in adult patients with low and intermediate risk myelodysplastic syndromes (MDS)	Comments noted. The technology brand name has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		The phase III study MEDALIST has assessed luspatercept for the treatment of anaemia in adult patients with very-low, low and intermediate MDS	
Population	British Society for Haematology and Royal College of Pathologists	No, the population in the scope is confusing. The scope states that the population is 'Adults with anaemia caused by MDS and have received or are not eligible for erythropoiesis-stimulating agent therapy'. However, the economic analysis states 'The use of luspatercept is conditional on the presence of ring sideroblasts. The economic modelling should include the costs associated with diagnostic testing for ring sideroblasts in people with MDS who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test'. So the population should tally with the economic analysis or reverse as it is confusing.	Comment noted. The population has been updated to specify the presence of ring sideroblasts.
	Celgene	Treatment of adult patients with very low, low or intermediate risk MDS associated anaemia who are ring sideroblast positive, are not del5q positive, require red blood cell transfusions and have received or are not eligible for erythropoiesis-stimulating agent therapy.	Comment noted. The population has been updated.
Comparators	British Society for Haematology and Royal College of Pathologists	The main comparator will be BSC. As the population is 'Adults with anaemia caused by MDS and have received or are not eligible for erythropoiesis-stimulating agent therapy' then a comparator not discussed is ESA in those that have not received an ESA due to not being eligible. In this situation it will include patients who have a low score for responding to an ESA, so very relevant. In the UK lenalidomide is used in ESA failure or ineligible MDS patients but only in del(5q), so not this population of patients. However, I believe it to be a relevant comparator in this setting. Rare patients may receive antitymocyte globulin or immunosuppression particularly in MDS – hypoplastic.	Comments noted. Following the scoping teleconference, ESA was considered an appropriate comparator for a small population within NHS clinical practice who have low chance of response to ESA (by MEDALIST trial inclusion criteria). Feedback from clinical experts confirmed that lenalidomide is not routinely used in NHS

Section	Consultee/ Commentator	Comments [sic]	Action
			clinical practice for non del(5q) patients and antitymocyte globulin or immunosuppression are not used for sideroblastic patients.
	Celgene	Lenalidomide would not be considered a comparator as the deletion 5q cytogenetic abnormality population was excluded from the MEDALIST trial.	Comment noted. Feedback from clinical experts confirmed that lenalidomide is not routinely used in NHS clinical practice for non del(5q) patients.
Outcomes	British Society for Haematology and Royal College of Pathologists	Most important outcome measures will be transfusion independence, duration of transfusion independence, haematological improvement (by the IWG 2006 criteria) and QOL, along with safety. I am not aware of overall survival being part of the Luspatercept trials.	Comment noted. The purpose of the outcomes section is to specify concepts needed to appraise the technology and not to identify specific criteria. Overall survival was listed as a secondary outcome in the clinical trials registry.
	Celgene	A reduction in RBC transfusion burden is a clinically meaningful outcome and should be considered	Comment noted. Transfusion burden has been added as an outcome.

Section	Consultee/ Commentator	Comments [sic]	Action
Economic analysis	Celgene	Current diagnostic procedures include testing for ring sideroblasts. Luspatercept initiation would occur after initiation of best supportive care, therefore further diagnostic testing and associated costs would not be required within the economic analysis. Related guidelines that should be considered are Revised IPSS for MDS Greenberg 2012 (blood) and BCSH Guidelines as in the references	Comment noted. Current BCSH guidelines state that presence of ring sideroblasts affects choice of treatment options and would therefore be considered as part of clinical practice. Costs of testing for ring sideroblasts have been removed from the scope.
Equality and Diversity	British Society for Haematology and Royal College of Pathologists	Not aware of any discrimination	Comment noted. No action required.
	Celgene	None identified	Comment noted. No action required.
Other considerations	Celgene	None identified	Comment noted. No action required.
Innovation	British Society for Haematology and Royal College of Pathologists	The treatment of lower risk MDS is an unmet need. Apart from lenalidomide in MDS del(5q) there have been little change to treatment for many years. It is welcome to the MDS community to have a new therapy which may improve QOL through reduction or no need for transfusions. The technology appraisal needs to spend significant time researching the data on BSC –	Comment noted. The company will have an opportunity to provide evidence on the innovative nature of its

Section	Consultee/ Commentator	Comments [sic]	Action
		transfusions with regards issues around QOL and the hazards of transfusion. The appraisal needs to look for subgroups that may benefit from the treatment in detail. This maybe available from the MEDALIST trial once published in its full form.	product in its submission. No action required.
	Celgene	MDS patients currently have few approved therapeutic options. Erythropoiesis-stimulating agents (ESAs) work on early stage of erythroid progenitor cells and, although often prescribed in MDS, have limited effect. In many patients with lower-risk MDS, anaemia will eventually become resistant to ESAs and will require repeated RBC transfusions. There is also a cohort of Low Risk MDS patients who are ineligible/ intolerant to ESAs. Long-term RBC transfusion dependence has several detrimental clinical effects including iron overload, and a negative impact on patients' quality of life (QoL). – Luspatercept works by targeting specific TGF-beta proteins involved in late-stage RBC maturation, stimulating RBC differentiation and thereby preventing 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.	Comment noted. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
Questions for consultation	Celgene	There are no licensed treatment options for adult patients with very low, low or intermediate risk MDS who have associated anaemia except RBC transfusions. Best supportive care (BSC) is outlined appropriately and iron chelation may also be considered as part of BSC. Other supportive treatment, such as platelets, GCSF and antibiotics may be used due to the complications associated with the disease.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	British Society for Haematology and Royal College of Pathologists	Questions raised on the scope for consultation: • Treatment options for patients failing/intolerant/not eligible for ESA: Mainly BSC +/- iron chelation therapy. Lenalidomide for patients with del(5q). Younger patients may be considered for stem cell transplantation if they are transfusion dependent. • How many patients would be eligible for Luspatercept? This needs further work. • Comparators have been discussed above. • Outcome measures are discussed above. • 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? MDS with ring sideroblasts suggested by Platzbecker et al, Lancet Oncol 2017 18:1338. This group can be looked at in more detail – EPO levels, number of rings, SF3B1 mutation +/-, karyotype, baseline other cytopenias, IPSS-R groups, transfusion burden. Most of this data may be available from MEDALIST trial results when in published form. • Where do you consider luspatercept will fit into the existing NICE pathway, Blood conditions? Blood and Bone Marrow Cancers	Comments noted. Please see sections above for changes to the scope.

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

Leukaemia Care