National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

Response to consultee and commentator comments on the draft remit, draft scope (pre-referral) and provisional matrix

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	NCRI Myelodysplasia subgroup	Yes	Comment noted.
	Celgene	We consider this an appropriate topic for appraisal by NICE.	Comment noted.
	MDS UK Patient Support Group	Yes. The general health and ability to contribute to society, in or out of work, are key elements. By reducing/eliminating transfusion dependence, all round efficiency of patient contribution is improved; quality of life for patients coming off regular transfusions is vastly improved; costs associated with NHS/Personal Social Services and transfusion dependency would be decreased greatly, for both patients and carers.	Comment noted. NICE will initiate an appraisal for this topic in its work programme if a referral is received from the Department of Health and all relevant cost and benefits will be taken into consideration.
Wording	NCRI Myelodysplasia subgroup	Yes	Comment noted.

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	Celgene	The remit correctly identifies the lenalidomide license in this population.	Comment noted. Guidance will only be issued in accordance with marketing authorisation. In particular it was noted that, unless the marketing authorisation specifies low risk and intermediate-1 risk deletion 5q MDS, there would be potential to look at groups with intermediate-2 and high risk deletion 5q MDS.
	MDS UK Patient Support Group	The clinical effectiveness of Lenalidomide has already been proved, internationally. Cost effectiveness, as always, is related, not only to the costs of providing the drug, but also the true all in costs of transfusions and the substantial amount of non productive, patient time time associated with the transfusions, typically 2.5 hours per unit of blood transfused.	Comment noted. All relevant costs and benefits will be taken into account during the appraisal. Please note that costs will be considered from an NHS and Personal Social Services perspective.
Timing Issues	NCRI Myelodysplasia subgroup	N/A	Comment noted.
	Celgene	Celgene has not yet filed with the EMA for a license in this indication. Although the filing is expected to take place in the latter half of this year, we are still uncertain as to the exact timings and nature of the filing. [redacted]	Comment noted.

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	MDS UK Patient Support Group	Lenalidomide has been available, internationally, for in excess of five years. The issue remains extremely urgent. The only treatment option for this particular group of patients is best supportive care (BSC) which includes blood transfusion, therefore appraisal of lenalidomide as a possible effective and specific treatment option is highly timely.	Comment noted. NICE will initiate an appraisal for this topic in its work programme if a referral is received from the Department of Health.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	NCRI Myelodysplasia subgroup	This is adequate	Comment noted.
	Celgene	Background information is sufficient for the purpose of a scoping exercise. However, we would emphasise that we find very limited evidence to support the use of chemotherapy at all in this group. In a report from the York Haematological Malignancies Research Network (HMRN) registry, none of the ten patients with deletion 5q syndrome MDS were given chemotherapy.	Comment noted. The clinical expert confirmed that chemotherapy would not be a relevant comparator for the low and intermediate-1 risk deletion 5q MDS group. The scope has been amended accordingly. It was noted, however, that unless the marketing authorisation explicitly specifies low risk and intermediate-1 risk deletion 5q MDS, there would be potential to look at groups with intermediate-2 and high risk deletion 5q MDS.
	MDS UK Patient Support Group	The information is generally accurate	Comment noted.
The technology/ intervention	NCRI Myelodysplasia subgroup	Yes	Comment noted.

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	Celgene	The description of the technology itself is accurate. However, we should point out that the main clinical trial did not compare lenalidomide to “placebo” but rather to a “standard care” regimen which included a placebo oral tablet as well as supportive care in the form of blood transfusions and other regimens designed to reduce the symptoms of transfusion dependence.	Comment noted. The scope has been amended to clarify this. Guidance will only be issued in accordance with marketing authorisation..
	MDS UK Patient Support Group	Yes.	Comment noted.
Population	NCRI Myelodysplasia subgroup	Yes	Comment noted.
	Celgene	The population description matches the anticipated license.	Comment noted.
	MDS UK Patient Support Group	This response relates only to patients exhibiting myelodysplasia through the 5q- deletion. This is the group of patients that were seen to benefit from this treatment in clinical trials.	Comment noted.
Comparators	NCRI Myelodysplasia subgroup	Yes	Comment noted.
	Celgene	We would comment that low-dose chemotherapy (LDC) and immunosuppressors are not appropriate comparators for this appraisal. Low-dose chemotherapy is not routinely used in del5q MDS nor indeed in any kinds of MDS which are considered low risk. The York HMRN registry found no cases of 5q syndrome MDS to have received LDC, although this registry only captured ten patients with the disease sub-type. Similarly, we do not have any information from the HMRN registry regarding the use of immunosuppressors agents, nor have we heard from clinicians that immunosuppressors are commonly used to treat this illness. Therefore we recommend that “best supportive care” be included as a main comparator. With regard to the best supportive care regimen, supportive care with red blood cell (RBC) transfusions remains the mainstay treatment for the majority of patients with 5q syndrome MDS. Frequent transfusions may be associated with	Comment noted. It was agreed at the Scoping Workshop that best supportive care, including blood transfusions, is the relevant comparator. The scope has been amended accordingly.

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		iron overload which subsequently require iron chelation therapy. Recombinant erythropoietin (EPO) with or without granulocyte colony stimulating factor (G-CSF) are less effective at improving transfusion dependency than in other forms of low-risk MDS. Serum erythropoietin levels are often higher in 5q-syndrome and when combined with the need for frequent transfusions, predict for poor response to EPO therapy. Significantly lower response rates are reported in MDS patients with del(5q) (up to 14%) as compared with other subtypes of low risk MDS (up to 37%). New EPO agents are currently under trial investigation but none are currently ready for launch. (Mohamedali, A.; Mufti G. J., 2009. Van-den Berghe's 5q- syndrome in 2008. British Journal of Haematology, Volume 144, Issue 2, pages 157–168) Erythropoietin is used in UK clinical practice with del5q MDS although we have little information about how much, or for how long. The York HMRN registry suggests that 4 of the 10 patients observed with 5q syndrome MDS received EPO. However, the small n makes it difficult to predict a national usage level. We are not aware of any clinical criteria by which patients might be pre-selected to receive EPO. The MDS-004 trial on which our economic model is based did not observe EPO use in its "standard care" arm. Therefore, EPO in this appraisal may be best considered as a sensitivity analysis adjustment to the "standard care" arm rather than as a formal comparator in its own right. A question was also asked in the draft scope as to whether stem cell transplantation would make a valid comparator. The simple answer is no. Stem cell transplantation (SCT) is a treatment choice which is usually made in patients deemed fit enough to attempt this curative option. Unlike in the high-risk group, patients with del5q are not facing imminent death so SCT, with its associated high risk of mortality, is generally not chosen lightly. There may be isolated cases where a clinician elects to attempt SCT with the patient's consent, but we do not feel that such cases need to be represented in an economic assessment of lenalidomide.	

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	MDS UK Patient Support Group	Yes, the options summarised may be applicable to the 5q- condition. The prime comparator is blood transfusion therapy, probably the `best alternative care'. However, BSC constitutes palliative care only but offers no therapeutic benefit.	Comment noted. It was agreed at the Scoping Workshop that best supportive care, including blood transfusions, is the relevant comparator. The scope has been amended accordingly.
Outcomes	NCRI Myelodysplasia subgroup	Yes	Comment noted.
	Celgene	The primary outcome of the main lenalidomide trial MDS-004 is the proportion of patients achieving transfusion independence for more than 182 consecutive days. Relevant secondary outcomes include: • Erythroid response • Change in blood haemoglobin levels • Duration of RBC independence • Change in platelet levels from baseline • Overall Survival • Progression to Acute Myeloid Leukaemia (AML) • Health-related quality of life as measured by a disease-specific quality of life scale	Comment noted. No change required to the scope.
	MDS UK Patient Support Group	Generally, yes. As with any drug, certain patients may exhibit side effects, but experience with clinical trials of Lenalidomide demonstrate that a substantial majority benefit from a resulting, all round improvement in quality of life.	Comment noted. No change required to the scope.
Economic analysis	NCRI Myelodysplasia subgroup	None.	Comment noted.

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	Celgene	We have no specific comments on the design suggested. However, we would re-emphasise our comment regarding to the valuation of transfusion independent health states.	Comment noted.
	MDS UK Patient Support Group	The proposed economic analysis is appropriate and the time horizon is sufficient to allow a proper evaluation.	Comment noted.
Equality and Diversity	NCRI Myelodysplasia subgroup	None.	Comment noted.
	Celgene	Lenalidomide in 5q syndrome MDS is not an end-of-life medicine. Therefore, it must be judged against the normal cost-effectiveness threshold with no adjustments made to utility values. Without adjustments, QALYs gained in the mostly elderly MDS patients are likely to be lower than those gained in younger populations. This represents a potential equality issue which Appraisal Committees must maintain awareness of in their deliberations, since the cost-utility approach will not account for it automatically. Failure to grant this issue due attention could result in the body of NICE guidance favouring interventions which deliver benefits to younger populations and leaving out the elderly. We are aware that NICE's own procedures contain instructions to give exactly this kind of consideration. There are no other significant equality issues as set out in this question.	Attendees at the Scoping Workshop agreed that this was not an equalities issue per se as the Method's Guide states that 'The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population.' It was noted as a general comment around QALY gains and utilities.
	MDS UK Patient Support Group	There would seem to be no differential disqualifying MDS 5q- patients through race, disability, religion, etc. On this basis, unlawful discrimination of any kind could be discounted.	Comment noted.

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Innovation	Celgene	We consider the technology to be an innovative step-change in the management of 5q syndrome MDS, on the following grounds: • Lenalidomide, in a field of high unmet need, delivers impressive results in terms of transfusion independence, blood haemoglobin level and overall survival. • The technology has an immunomodulatory mode of action which is not found in any other treatment licensed for this disease. • The product has an oral formulation which means that patients who achieve transfusion independence can remain at home and reduce their number of visits to hospital.	Comment noted. It was noted at the Scoping Workshop that the mode of administration, the potential size of the gains and the fact that this is the first treatment in an area of high unmet need, indicates potential for it to be an innovative treatment option. The Appraisal Committee will take these factors into account in the course of the appraisal.
	NCRI Myelodysplasia subgroup	*Do you canister 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 management of the condition)?* Yes.	Comment noted.
	MDS UK Patient Support Group	This technology is definitely innovative and does result in significant and substantial changes for this group of patients, relieving them of the burden of frequent blood transfusions. This drug is the only specific treatment for this particular group of patients with this condition. The health related benefits may be summarised: Reduction in levels of fatigue and breathlessness. Substantial savings in patient and hospital time associated with blood transfusion. Elimination of the discomfort and inconvenience of treatment for iron overload, with attendant cost saving. Huge improvement in patient quality of life.	Comment noted. It was noted at the Scoping Workshop that the mode of administration, the potential size of the gains and the fact that this is the first treatment in an area of high unmet need, indicates potential for it to be an innovative treatment option. The Appraisal Committee will take these factors into account in the course of the appraisal.

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Other considerations	NCRI Myelodysplasia subgroup	None.	Comment noted.
	MDS UK Patient Support Group	No additional suggestions.	Comment noted.
Questions for consultation	MDS UK Patient Support Group	The need for a specific treatment for the MDS 5q- deletion condition is both immediate and long standing.	Comment noted. NICE will initiate an appraisal for this topic in its work programme if a referral is received from the Department of Health.
	Celgene	*Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* The health states of transfusion dependence and independence are crucial to our modeling. To date they have been evaluated in one study (1. Szende A, Schaefer C, Goss TF et al. Valuation of transfusion-free living in MDS: results of health utility interviews with patients. Health Qual Life Outcomes 2009; 7: 81.) However, as NICE have acknowledged in their recent appraisal of azacitidine, economic models in this disease area may not fully capture the total health benefits associated with attaining transfusion independence. Freedom from blood transfusions has powerful psychological benefits which we are difficult to capture using an EQ-5D instrument or any adaptation thereto. The burden associated with blood transfusions both for patients and their carer's are unlikely to be well captured through a simple mapping of clinical trial QoL scores to EQ-5D. The convenience afforded by the oral formulation of lenalidomide is also associated with significant benefits, some health-related, which are unlikely to be captured well in EQ-5D metrics. Reducing the transfusion burden on hospitals can also have knock-on effects within the NHS by freeing up additional resources. We will endeavour to provide further evidence during the appraisal to further illuminate this issue.	Comment noted. It was noted at the Scoping Workshop that a number of benefits such as the value of preserving blood supplies, the increased quality of life with transfusion independence and the improved quality of life due to reduced carer burden would be excluded from QALY gains and the Appraisal Committee will include these considerations in their discussions.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Celgene	No comments	Comment noted.

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

Novartis Pharmaceuticals
Royal College of Nursing
Welsh Assembly Government
Department of Health
Marie Curie Cancer Care

Comment 2: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Add Allied Health Professionals Federation to General Commentators	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
2.	Remove Chinese National Healthy Living Centre from patient/carer group consultees.	NICE Secretariat		Removed	The Chinese national Healthy Living Centre has requested only to be involved in Chinese related topics.
3.	Remove CancerACTIVE from patient/carer groups.	NICE Secretariat		Removed	This organisation has disbanded. CANCERactive has been removed from the matrix of consultees and commentators.

4.	Remove British Oncological Association (BOA) from professional groups.	NICE Secretariat		Removed	This organisation has disbanded. The British Oncological Association (BOA) has been removed from the matrix of consultees and commentators.
5.	Remove Policy Research Institute on Ageing and Ethnicity	NICE Secretariat		Removed	This organisation has requested to be removed from all matrices.
6.	Add Chronic Myeloid Leukaemia Support Group to patient/carer groups.	PPIP		Added	Chronic Myeloid Leukaemia Support Group meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group consultee.