NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Myelodysplastic syndrome (deletion 5q) - lenalidomide [ID480]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Celgene	Celgene is pleased that the Committee recognises that on the basis of the evidence on transfusion independence and health-related quality of life, lenalidomide is a clinically effective treatment for people with MDS associated with a deletion 5q cytogenetic abnormality (MDS del(5q)). This was recently also recognised by the Cancer Drug Fund in evaluating lenalidomide in this patient population, endorsing the benefit for patients in England. Celgene would once again like to draw to the attention of the Committee, that MDS del(5q) continues to be an area of high unmet need. Currently there are no other treatment options available barring best supportive care consisting of regular blood transfusions, treatment of transfusion related side effects and management of disease associated morbidity.	Comments noted. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15).
Celgene (continued)	Celgene is disappointed that the ACD presently doubts as to whether lenalidomide improves survival in these patients and concludes it is not cost-effective when based on Celgene's health economic analyses, or following the additional analyses performed by the ERG.	Comments noted.The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15). However, the Committee concluded that the most plausible ICER was approximately £70,000 per QALY gained, and therefore lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality could not be recommended as a cost-effective use of NHS resources.
Celgene (continued)	Following consideration of the content of the ACD and the Evidence Review Group Evaluation Report (ERGR), Celgene have structured an evidence-based response to the key issues which appear to have driven the Committee's recommendation: • Transfusion dependency status as the primary prognostic factor, determining overall survival and the rate of progression to AML. • Time to iron chelation initiation (as assumed to be at 8 weeks post treatment initiation in the economic model). • Clinical monitoring of MDS (haematologist or GP). • Assumptions on utility scores, based on either a mapping of EQ-5D values (from MDS-004 trial data) or published estimates (Szende et al.) • Methodology used to produce estimates of survival and AML due to trial crossover.	Comments noted. Please see below for full response to the issues raised here on transfusion dependence (see FAD section 4.6 and 4.7), iron chelation (FAD section 4.12), monitoring (see FAD section 4.11), utility (see FAD section 4.13) and crossover methodology.

Consultee	Comment	Response
Celgene (continued)	Celgene have provided a set of supplementary information regarding the association between transfusion independence, survival and progression to AML, based on a systematic literature review, and has explained this further from the following evidence-based dimensions • Baseline red blood cell transfusion dependence (RBC-TD) is associated with increased risk of non-leukaemic death and also more advanced disease, leading to increased risk of AML and hence leukaemic death. • In addition, the reversal of RBC-TD to red blood cell transfusion independence (RBC-TI) leads to improved survival because by correcting severe anaemia and reducing the need to transfusions, non-leukaemic mortality is reduced through the avoidance of complications of anaemia.	Comments noted. The Committee considered the evidence from MDS-004 on overall survival and transfusion independence, the additional information submitted by the manufacturer at consultation and comments from the ERG. It concluded that it is reasonable to assume an association between transfusion independence and increased overall survival, although there remains uncertainty about the exact strength of this relationship and whether this relationship diminishes over time (see FAD section 4.6)
Celgene (continued)	In response to the critique from the ERGR, and the ACD, Celgene has made a number of amendments to the cost effectiveness analysis. We have provided a re-analysis of the base case and associated sensitivity analysis for consideration by the Committee. Finally, Celgene has provided brief clarification on the appropriateness of utility score mapping and trial crossover adjustment, which were discussed during the appraisal committee meeting. Celgene would urge the Committee in its reconsideration of the ACD to note the clarifications / changes to the economic modelling that have been made to address the key concerns raised in the ACD. We believe these clarifications now allow for an accurate and valid cost-effectiveness assessment.	Comments noted. The Committee has considered the evidence from MDS-004, the additional information submitted by the manufacturer at consultation and comments from the ERG. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15). However, the Committee concluded that the most plausible ICER was approximately £70,000 per QALY gained, and therefore lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality could not be recommended as a cost-effective use of NHS resources.
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **Transfusion independence as a prognostic factor** **Summary of the issue** • The Committee was unclear on the model's use of transfusion dependency status as the primary prognostic factor, determining overall survival and the rate of progression to acute myeloid leukaemia (AML). • Having taken into account clinical specialist opinion, the Committee was of the opinion that transfusion independence measured at 8 weeks would not lead to a survival gain in the long term, and that the effect of lenalidomide on reduced transfusion dependence would not attribute any benefit in terms	

Consultee	Comment	Response

	of a reduced rate of progression to AML.
	Summary of response
	• In order to better highlight the association between transfusion dependence /independence and survival, a systematic literature review was performed in July 2013.
	  ○ A substantial body of literature was reviewed and found to provide support for a relationship between transfusion dependence and shortened survival through multiple mechanisms.
	  ○ Evidence also supports the argument that becoming transfusion independent following dependency at baseline leads to improved survival
	• The association between lenalidomide treatment and reduced rate of progression to AML is supported from evidence which shows:
	  ○ Baseline RBC-TD or severe anaemia is associated with more advanced disease and leads to increased risk of AML progression.
	  ○ In many MDS del(5q) patients, lenalidomide treatment leads to clonal suppression resulting in reduced risk of AML. The clonal suppression often also results in TI.
		Comments noted. The Committee considered the evidence from MDS-004 on overall survival and transfusion independence, the additional information submitted by the manufacturer at consultation and comments from the ERG. It concluded that it is reasonable to assume an association between transfusion independence and increased overall survival, although there remains uncertainty about the exact strength of this relationship and whether this relationship diminishes over time (see FAD section 4.6).
		
		The Committee considered the evidence from MDS-004 on AML progression and transfusion independence, the additional information submitted by the manufacturer at consultation and comments from the ERG. It noted that the manufacturer had submitted additional information on the rationale for lenalidomide in slowing progression to AML, which included literature that showed a relationship between transfusion status and risk of progression to AML, and also evidence from the pivotal trials, including MDS–004, showing transfusion status was a statistically significant variable for AML progression. The Committee noted, however, that the ERG had highlighted there was also evidence from MDS-004 to show that transfusion status was not a significant variable for progression to AML. The Committee also noted the safety briefing that had been sent by the manufacturer to healthcare professionals about the use of lenalidomide for MDS, which outlined a 2-year risk of progression to AML of 13.8% in MDS associated with a deletion 5q cytogenetic abnormality. The Committee understood that this was similar to the natural history rate. As a result, the Committee there was considerable uncertainty over whether lenalidomide

Consultee	Comment	Response
		impacted on rates of progression to AML, and therefore that it was unreasonable to assume that lenalidomide reduced progression to AML (see FAD section 4.7).
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **Implementing revisions to the economic model** **Summary of the issues** • The Committee indicated that the monitoring of patients with MDS would be performed by a haematologist, rather than by a general practitioner, as assumed in the submitted base-case model. • The Committee accepted comments from the ERG regarding the modelling of iron chelation; that the time to iron chelation initiation is more likely to be at 16 weeks rather than the modelled 8 weeks. The ERG applied this change due to uncertainty regarding a calculation in the electronic model for the threshold at which iron chelation therapy is required for transfusion dependent patients. • The Committee were not convinced of the appropriateness of transfusion dependency as a factor in determining the rate of progression to AML. **Summary of response** • The sensitivity of base-case model results to the Committee's recommendations was investigated. The impact on the model results of routine MDS monitoring being performed by a haematologist rather than a GP was assessed. The base case incremental cost-effectiveness ratio (ICER) becomes £65,153 (versus a submitted ICER of £62,674.). • Secondly, the threshold at which iron chelation therapy begins was extended from 8 weeks to 16 weeks. This change was made in addition to the assumption of monitoring by a haematologist, , increasing the ICER further to £69,901. ○ The assumption of an iron chelation threshold of 16 weeks rather than 8 comes from a labelling error in the model. The original value for RBC units was for the preceding 4 weeks, incorrectly labelled as the preceding 8 weeks. This value was multiplied by 2, assuming a constant transfusion rate over the preceding 8-week period in full.	Comments noted. The Committee accepted the revisions to the economic model for monitoring by a haematologist rather than a GP (see FAD section 4.11). The Committee accepted that the economic model contained a labelling error, and that the model required no adjustment for iron chelation (see FAD section 4.12).

Consultee	Comment	Response
	• To test the impact of the removal of any benefit of lenalidomide on the rate of progression to AML, the modelled rate was set equal to that of transfusion independent patients for all patients. This was applied in addition to the above 2 assumptions of monitoring by a haematologist. Resulting incremental quality-adjusted life years (QALYs) are 0.72 and the ICER becomes £68,125. ○ This model revision is also likely to be inappropriate. Literature suggests that the Committee's view of there being no link between transfusion independence and reduced AML progression ignores a key area in which transfusion dependency is an important prognostic factor.	The Committee considered the evidence from MDS-004 on AML progression and transfusion independence, the additional information submitted by the manufacturer at consultation and comments from the ERG. It noted that the manufacturer had submitted additional information on the rationale for lenalidomide in slowing progression to AML, which included literature that showed a relationship between transfusion status and risk of progression to AML, and also evidence from the pivotal trials, including MDS–004, showing transfusion status was a statistically significant variable for AML progression. The Committee noted, however, that the ERG had highlighted there was also evidence from MDS-004 to show that transfusion status was not a significant variable for progression to AML. The Committee also noted the safety briefing that had been sent by the manufacturer to healthcare professionals about the use of lenalidomide for MDS, which outlined a 2-year risk of progression to AML of 13.8% in MDS associated with a deletion 5q cytogenetic abnormality. The Committee understood that this was similar to the natural history rate. As a result, the Committee concluded it was uncertain if lenalidomide impacted on rates of progression to AML, and therefore that it was unreasonable for the economic model to assume that lenalidomide reduced progression to AML (see FAD sections 4.7 and 4.10).

Consultee	Comment	Response
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **Further information on utilities used in the submission** **Summary of the issue** • During the appraisal meeting the Committee requested additional information on the mapping from FACT-An scores to EQ-5D. **Summary of response** • Regression models were generated using both FACT-An summary scales and FACT-An individual items to predict EQ-5D utility. • All models produced had a high mean absolute error indicating that they were not accurate predictors of EQ-5D utility. • Additionally the items used within the best fitting mapping did not include the items which showed large variation based upon transfusion dependency status. The relative reduction in TD scores compared to TI scores using the total FACT-An score was substantially greater than for all items included in the best mapping model evaluated • As such, a strong argument is presented for not using the mapped EQ-5D values in modelling the MDS-004 trial data; and using instead more sensitive utility scores from a source such as Szende et al (2009).	Comments noted. The Committee concluded that the utility values used in the manufacturer's model were a reasonable reflection of the impact of transfusion status on health-related quality of life in people with MDS (see FAD section 4.13).

Consultee	Comment	Response
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **Trial crossover analysis** **Summary of the issue** • Uncertainty was raised by the Committee around the methodology used to produce estimates of survival and AML due to trial crossover. **Summary of response** • The two-stage Weibull method used to analyse crossover was selected based upon a paper by Latimer et al. (2013) analysing various methods of adjusting for crossover • Rank-preserving structural failure time models (RPSFTM) were not used as the method relies on an underlying assumption of exchangeability which may not uphold in oncology due to potential changes in the underlying characteristics of subjects at the point of crossover relative to randomisation • Inverse probability of censoring weights (IPCW) was not used as this method assumes there are no unmeasured confounders predictive of switching or death. This approach has been found to produce biased estimates even if all common predictors are taken into account if the study sample size is small or there is strong selection bias. As the MDS-004 trial contained only a small sample size the method was not considered appropriate.	Comments noted. The Committee accepted that the two-stage Weibull method was the most appropriate method for adjusting for cross over.
Myelodysplastic Syndromes UK	4.9 Though lenalidomide confers no advantage over BSC in respect of time of progression to AML, the important issue for patients is the improvement in their quality of life. It is our universal experience that transfusion dependent patients are far more concerned about the quality of the life that they have rather than its overall duration. The fact that the time for progression to AML is not altered by lenalidomide is not an issue for patients who have to travel to hospital several times a month to receive frequent transfusions, but still suffer from poor energy, due to low haemoglobin levels. These patients are unable to have a normal day to day life – as opposed to patients on lenalidomide, whose haemoglobin levels have stabilised.	Comments noted. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15).

Consultee	Comment	Response
Myelodysplastic Syndromes UK (continued)	4.13 The ICER calculations are widely varied. The reason for this appears to be the range of scenarios considered in terms of transfusion dependence/independence. Some of the calculations are extrapolated from data involving a small number of patients. In the discussion at the appraisal the committee appeared to be disagreeing with the results of the ERG analysis. This disagreement appears to be reflected in the ACD which makes the spread of ICERs too broad to allow a sensible decision to be made. The level of the ICER may become critical should a Patient Access Scheme be introduced. We ask that the committee considers this in setting and agreeing an ICER as the present divergent values may render lenalidomide too costly to be available to those patients who can benefit from it.	Comments noted. Additional information was submitted by the manufacturer at consultation with the aim of reducing the uncertainty in the ICER (see FAD sections 3.42 and 3.43). The Committee concluded that the most plausible ICER was approximately £70,000 per QALY gained, and therefore lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality could not be recommended as a cost-effective use of NHS resources.
Myelodysplastic Syndromes UK (continued)	4.14 The emphasis here is entirely on overall length of survival with no consideration for quality of life during treatment, which is of paramount importance to patients. The issue is quality of life over a much shorter period of a few years rather than the twenty years used in the model.	Comments noted. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits. The Committee considered that this was already captured in the QALY calculation and that there were no additional gains in health-related quality of life over those already included in the QALY calculations (see FAD section 4.2 and 4.15).
Royal College of Physicians	**Has all of the relevant evidence been taken into account?** The evidence base available to inform a precise ICER calculation is very limited and much of this is extrapolation. To our knowledge there is no more relevant evidence.	Comments noted. No action required.
Royal College of Physicians (continued)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Clinical effectiveness** The Appraisal Committee acknowledges the clinical effectiveness of lenalidomide for this indication specifically in promoting independence from red cell transfusion. The magnitude of haemoglobin response is not noted in the ACD but we believe was mentioned by the clinical expert in committee. This is worth noting given that the magnitude of haemoglobin increase, which is sustained by lenalidomide, is not normally achieved by alternative strategies to improve anaemia such as red cell transfusions or ESAs. Indeed red cell transfusion produces a cyclical symptomatic benefit but peak haemoglobin concentrations are rarely >110 g/l which are achieved for perhaps only one week in the typical four week cycle. In contrast most responders to lenalidomide achieve sustained haemoglobin concentrations >110 g/l for a median response duration of	Comments noted. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15).

Consultee	Comment	Response
	around 2 years. The Committee clearly placed considerable emphasis on the comment by the clinical expert that although red cell transfusion dependence is an adverse risk factor for overall survival in MDS, it remains unclear if reversal of transfusion dependence can in turn overcome that decrement in overall survival. This statement is correct but there are data that can be extrapolated from other treatments for anaemia in low-risk MDS, which indicate that responders to therapies that increase haemoglobin concentration may have improved survival compared with untreated patients. Such retrospective cohort comparisons have been published for ESA1,2 and for antithymocyte globulin3. If this were correct, despite the methodological limitations of such comparisons, then it is plausible that lenalidomide could produce a similar benefit, particularly as the median duration of response to lenalidomide is similar to that of ATG and of ESAs. Naturally, it could be that these drugs select (responding) patients who will have a better overall survival without therapy but the same is true for any drug that is demonstrated to improve the overall survival of any ITT clinical trial test arm vs. control. In section 4.14 the Committee consider that lenalidomide is not a 'step change' in the management of symptomatic anaemic patients with MDS and del(5q) because there is no clear evidence of an overall survival advantage. Our experts believe that Lenalidomide is a step change given the very high response rate and magnitude of haemoglobin increase in these patients. Because the dataset available to assess the clinical and cost effectiveness is very limited it is rather premature to deem this therapy to not be such a step change. We believe that this statement should be softened. The Committee have chosen not to seek subgroups in which the benefit may be greater with lenalidomide. An example would be patients with platelets > 150 x 109/l who consistently have a higher response rate in all published series.	Comments noted. The Committee considered the evidence from MDS-004 on overall survival and transfusion independence, the additional information submitted by the manufacturer at consultation and comments from the ERG. It concluded that it is reasonable to assume an association between transfusion independence and increased overall survival, although there remains uncertainty about the exact strength of this relationship and whether this relationship diminishes over time (see FAD section 4.6).

Consultee	Comment	Response
Royal College of Physicians (continued)	**Cost effectiveness** Although not health economists we would like to make some comments regarding assumptions made by the company and by the ERG • We are unclear why the company have used data from the 5mg lenalidomide arm to approximate response duration to BSC given that the response rate is still much higher than the BSC group itself and the duration of response appears to be similar to that of the 10mg lenalidomide arm (Figure 6 on p64 of Manufacturer's Submission)? • In 3.27 ' It also noted that 1 dose reduction in the lenalidomide 10 mg group meant that patients received effectively the same dose as the 5 mg group.' This statement is incorrect; the median doses after 4 cycles were 5m in the 10mg arm and 2.5mg in the 5mg arm. Furthermore, one of the reasons for a higher response rate in the 10mg arm is likely to be dose intensity in the first cycle, which is clearly dose dependent and different between the two arms. It is therefore wrong to assume that doses were 'effectively' the same in both arms for patients who had one dose reduction in the 10mg arm. This does not affect the economic model significantly given that the cost of different tablet doses is similar. Dose interruptions (which would affect the differential costs between the both arms were it imbalanced) were more frequent in the 10mg arm than the 5mg arm.	Comments noted. The manufacturer explained that they used data from the 5mg lenalidomide group for best supportive care as insufficient numbers in the placebo arm responded to treatment (see FAD section 3.15). Section 3.27 has now been updated.
Royal College of Physicians (continued)	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** There is considerable uncertainty surrounding the modelling, primarily due to a lack of high quality utility and survival data. We do not consider the provisional recommendations to be 'sound' given these uncertainties but can understand that the ICER is not likely to be close to £30,000.	Comments noted. Additional information was submitted by the manufacturer at consultation with the aim of reducing the uncertainty in the ICER (see FAD sections 3.42 and 3.43). The Committee concluded that the most plausible ICER was approximately £70,000 per QALY gained, and therefore lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality could not be recommended as a cost-effective use of NHS resources.

Consultee	Comment	Response
Royal College of Physicians (continued)	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity** There is potential discrimination for MDS patients with del(5q) from the Jehovah's Witness community who will refuse blood product support for their anaemia and who could reasonably be expected to respond to lenalidomide. **References** 1. Park S, Grabar S, Kelaidi C, et al: Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 111:574-82, 2008 2. Jadersten M, Malcovati L, Dybedal I, et al: Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26:3607-13, 2008 3. Sloand EM, Wu CO, Greenberg P, et al: Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26:2505-11, 2008.	Comments noted. The Committee noted that no representations had been made or evidence received about the pathway of care for this particular group of patients, or about the effectiveness of lenalidomide in this patient population. Therefore the Committee agreed that it would not be appropriate to make recommendations for a subgroup of patients unable to receive blood transfusions.

Consultee	Comment	Response
Royal College of Pathologists	1) The decision of the Committee might legitimately be perceived to be discriminatory to individuals who choose not to receive blood products on religious grounds (i.e. Jehovah's Witnesses). While this may not be unlawful it is nonetheless worthy of highlighting as the document makes no mention of this scenario.	Comments noted. The Committee noted that no representations had been made or evidence received about the pathway of care for this particular group of patients, or about the effectiveness of lenalidomide in this patient population. Therefore the Committee agreed that it would not be appropriate to make recommendations for a subgroup of patients unable to receive blood transfusions.
Royal College of Pathologists (continued)	2) There is an apparent inconsistency of recommendation here between the use of Lenalidomide in 5q- syndrome and in multiple myeloma that is not clearly explained. These are both malignant haematological conditions for which Lenalidomide is highly effective therapy and yet the few patients with 5q- syndrome are clearly being treated differently to the many patients with myeloma. On face value this appears to be discriminatory by valuing patients with one form of cancer above another despite good evidence to show similar levels of efficacy and improvements in quality of life for both conditions treated with Lenalidomide.	Comments noted. There are several differences between this appraisal and TA171. TA171 recommends lenalidomide for multiple myeloma, however only after 2 prior therapies. Additionally, TA171 is recommended only with a PAS Finally, lenalidomide in the appraisal for multiple myeloma is considered an end of life drug, therefore the ICER threshold is higher.
Royal College of Pathologists (continued)	3) It is my considered view that the estimated incremental cost-effectiveness ratio (ICER) for lenalidomide of greater than £70,000 per QALY gained is excessive and fails to appropriately take into consideration the benefits of quality of life improvements in patients with 5q- syndrome.	Comments noted. Additional information was submitted by the manufacturer at consultation with the aim of reducing the uncertainty in the ICER (see FAD sections 3.42 and 3.43). The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15). The Committee considered that this was captured in the QALY calculation and that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Myelodysplastic Syndromes UK	I just wanted to confirm that I agree with Rodney's comments. I must admit that as a patient the meeting and also the resulting document there were aspects of this process that I found very technical and sometimes difficult to understand at times due to the medical terminology etc. I am also a little frustrated as a patient that this process seems to be based purely on one study whereas there must be a lot more information available on the benefits of this drug.	Comments noted. Your comments regarding the meeting will be fed back to the Programme Team. The manufacturer performed a systematic review of the evidence on the clinical effectiveness of lenalidomide and comparator therapies for patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality whose condition is red blood cell transfusion dependent. The review identified a single phase III, randomised, double-blind, placebo-controlled trial (MDS 004), which compared lenalidomide 10 mg (n=69) and lenalidomide 5 mg (n=69) with placebo (n=67). Additional information was submitted by the manufacturer at consultation with the aim of reducing the uncertainty in the ICER (see FAD sections 3.42 and 3.43).
Myelodysplastic Syndromes UK (continued)	I know that Rodney has commented on section 4.14 but I also wanted to add a comment. This paragraph states that there was "no observed gain in survival with lenolidamide in the MDS-004 study". I know that for me personally this drug has definitely slowed down the progression of my disease, which in a younger patient is vitally important. It will therefore definitely contribute to a much greater gain for my survival rate as it currently staves off the need for other more risky treatments such as bone marrow transplants etc.. Therefore this is why I think just relying on one study doesn't show the whole picture.	Comments noted. The Committee agreed that lenalidomide is innovative in its potential to make a significant and substantial impact on health-related benefits (see FAD section 4.2 and 4.15).