NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality

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.

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.

Comments received from consultees

Consultee	Comment	Response
Celgene	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] Celgene is grateful for the opportunity to respond to the second Appraisal Consultation Document (ACD2) developed by the Appraisal Committee (the Committee) following its meeting on 1st April 2014. We are of course disappointed that the Committee was unable to recommend lenalidomide as a treatment option for the small cohort of patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality. However, we would like to take this opportunity to address the issues raised in ACD2, and remain hopeful that the Committee will review its preliminary recommendations and produce final guidance to the NHS that supports the use of lenalidomide as a clinically and cost-effective treatment for this group. I should say that we do feel that there has been a loss of focus on the patient throughout this lengthy appraisal process. This is particularly notable in Section 4.16 of ACD2: *"The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions offered a step change in treatment."* The Committee goes on to conclude that this convenience is incorporated in the QALY calculations, in a way that implies that the oral administration of lenalidomide is its only innovative feature. During the previous NICE consultation process patient groups and the Royal College of Physicians	Comment noted. Lenalidomide is recommended as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that, the convenience of a new oral treatment and reduction in the need for blood transfusions meant that lenalidomide offered a substantial step change in treatment. See section 4.14 of the Final appraisal determination (FAD).

Consultee	Comment	Response
	noted additional important aspects, over and above its oral administration. These included alleviation of depression and anxiety; improved ability to lead a normal life; high response rate and the magnitude of haemoglobin increase none of which are likely to be entirely captured by the QALY calculation. These benefits are recognised by national Cancer Drugs Fund decision summary scores,[1] which show that since April 2013, lenalidomide for MDS with isolated deletion 5q cytogenetic abnormality was the only application to have scored maximum points for meeting an unmet need and for its health related quality of life (HRQL) benefit out of the 57 applications that have made to the CDF to date. Ultimately, the Committee concluded that following updated analyses and with a lenalidomide patient access scheme (PAS) the 'final' incremental cost-effectiveness ratio (ICER) for consideration is £25,300, but that this figure was subject to uncertainty. As a result the Committee concluded that the actual figure may exceed £30,000. We think it is both unreasonable and unfair of the Committee to cite uncertainty here given that the MDS-004 study is the largest trial conducted in patients with this small subset of MDS, which is in itself an orphan disease (only 6.3% of MDS patients having del(5q)).[2]	The 'Considerations' section of technology appraisal guidance highlights areas of uncertainty that have arisen during discussions of the evidence (see NICE Guide to the methods of technology appraisal section 6.1.4). The survival estimates in the model were uncertain and therefore so was the proportion of people who would remain on treatment after 26 cycles to become eligible for the patient access scheme, and therefore the cost savings to the NHS under this scheme were uncertain. The Committee agreed that the ICER was uncertain but accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] In order to address the specific concerns raised by the Committee regarding this uncertainty, we have structured our response to focus on the following 3 issues: **1. Generalisability of the MDS-004 study population** **2. Uncertainty in cost-effectiveness results with incorporation of the patient access scheme** **3. Logistics of the patient access scheme**	Comments noted. The Committee agreed that although there were differences between the trial and marketing authorisation populations, on balance, the study was generalisable to the marketing authorisation population, and how lenalidomide would be used in clinical practice. See section 4.3 of the FAD.

Consultee	Comment	Response
	1. Generalisability of the MDS-004 study population In the Final Appraisal Document (FAD) issued in October 2013 the Committee concluded that the MDS-004 study population was generalisable for appraising lenalidomide for the relevant MDS del(5q) patient population. The Committee however effectively reverses this conclusion in ACD2, stating that generalisability to the licensed population is limited. Given that no additional related evidence was provided to affect the conclusion reached in the FAD, this development in ACD2 lacks transparency and appears to us to be perverse. Specifically, the proportion of patients who received prior erythropoiesis-stimulating agent (ESA) in MDS-004 was highlighted as the key factor reducing generalisability. The assumption underpinning this appears to be that prior ESA use is a condition of the lenalidomide license and that prior ESA use impacts prognosis. Both of these assumptions are, in fact, incorrect. The lenalidomide license does not state any requirement for prior ESA use. The license states that lenalidomide is “indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.” In the UK, as reflected in the trial, many patients are unlikely to receive prior ESA as it is widely recognised as an inadequate treatment for transfusion dependent MDS del(5q) patients.[2] ESA use in the UK is also limited by funding as no standard recommendation is available.[3] Additionally, prior ESA use has been shown not to be a statistically significant prognostic factor. Clinical feedback accepted as part of the Scottish Medicines Consortium (SMC) process indicated, that MDS-004 study patients were representative of the population that would be treated with lenalidomide in Scotland, both in terms of baseline characteristics (e.g. prior erythropoietin) and demographic characteristics. As such, we feel that there is sufficient evidence for the Committee to have confidence in the generalisability of the MDS-004 study and that any conclusion to the contrary would be hard to justify.	

Consultee	Comment	Response
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **2. Uncertainty in cost-effectiveness results with incorporation of patient access scheme** In ACD2 the Committee took a view that uncertainty in the strength of the relationship between achieving transfusion independence (TI) and extended overall survival (OS) contrived to make the proportion of patients becoming eligible for free of charge lenalidomide through the PAS uncertain. Celgene have previously provided a body of evidence to support the association between TI and OS, including the results of a systematic literature review. This is now further supported by a recent systematic review and meta-analysis conducted by the School of Health and Related Research (ScHARR) at the University of Sheffield, which associated TI with a 57% decrease in the risk of death compared to transfusion dependent patients.[4] Data collected as part of Celgene's lenalidomide Treatment Continuation Scheme (TCS), which includes patients with more severe characteristics (e.g. intermediate-2 and high risk) than permitted by the lenalidomide marketing authorisation, show that 28% of UK patients continued to receive lenalidomide at 26 cycles: comparable to the predicted figure of 31.9%. All of this represents conclusive evidence that supports the achievability of the outcomes projected for patients receiving lenalidomide. That the Committee have failed to recognise this evidence is surely both unfair and unreasonable. Additionally, some patients within the TCS database have received up to 70 cycles of treatment: without the benefit of a PAS and at full cost to the NHS. Recently published evidence from MDS-004 demonstrates a continued link between TI and OS for up to 7 years, and importantly lenalidomide becomes cost-effective at a model time horizon of between 5 and 6 years (over which time the relationship is shown to persist with considerably greater certainty).	Comments noted. The Committee noted that, if the proportion of people who reached 26 cycles was less than 27%, the ICER would be greater than £30,000 per QALY gained. It agreed that the ICER was uncertain but accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.

Consultee	Comment	Response
Celgene (continued)	[THIS IS A SUMMARY OF CELGENE'S COMENTS – PLEASE SEE CELGENE'S FULL RESPONSE TO THE ACD] **3. Logistics of the patient access scheme** The lenalidomide PAS was approved by the Department of Health following review by the Patient Access Schemes Liaison Unit (PASLU), whose remit is to review and evaluate PAS proposals regarding a scheme's value for the NHS.[5] This was an involved process with expert panel review meetings with clinicians and pharmacists present, and requests for clarifications from the manufacturer. The scheme was recommended only after PASLU were satisfied that the lenalidomide PAS was achievable. More specifically it was clinically robust, plausible, appropriate, feasible to implement and monitorable.[6] The PAS functions on the back of the pregnancy prevention programme (PPP) which is a mandatory requirement for prescribing lenalidomide. This approach has neutral burden on the NHS and dispensing pharmacists. With regards to treatment interruptions increasing uncertainties, it is already noted in the FAD that treatment interruptions were accounted for in the cost-effectiveness analysis through previous clarifications provided, and have minimal impact on the lenalidomide ICER. In summary, Celgene is disappointed that the Committee has decided to reverse its earlier conclusions around it's evidence consideration, which appears to us to have been undertaken unfairly and without the benefit of additional evidence; resulting in a negative ACD2. Celgene would like to emphasize again that MDS del(5q) is an orphan condition affecting a very small patient population (≈350 patients per annum in England and Wales) for whom there are no other treatment options. The robustness of the clinical and cost-effectiveness evidence that Celgene have provided is far more than would normally be possible for such a rare condition. We request that the emphasis of this process should therefore primarily be on the patient and enhancing access to innovative treatments, especially when they have already demonstrated cost-effectiveness.	Comments noted. .The Committee understood that patient access schemes are pricing agreements between the manufacturer and the Department of Health. The Committee acknowledged that there may be some uncertainty about the actual costs of lenalidomide paid in the NHS, but that it had no authority to assume a different cost than that agreed between the manufacturer and the Department of Health. The Committee accepted that that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.

Consultee	Comment	Response
	Celgene is, of course, committed to ensuring that patients are ultimately able to gain access to this treatment on the NHS and we shall engage fully in those of the Institute's formal processes that remain open to us. Thank you once again for the opportunity to respond to the recent ACD and we look forward to the ensuing discussions at the next Committee meeting.	
Myelodysplastic Syndromes UK/Leukaemia CARE	Please see below our response to the latest ACD for this appraisal. As we are addressing a variety of issues and sending further documents with our response, we have summarised the different points below. A. ACD Comments 1. Survival Benefit issue (ACD 4.3, 4.5, 4.9, 4.10, 4.12, 4.15) 2. PAS administration issue (ACD 4.13) 3. Sub-group of patients for lenalidomide B. Additional comments and documents 1. Additional patient statements – Appendix 1 2. Northern Ireland Assembly - MP David McIlveen 3. Small population issue 4. Scotland – SMC - Regional discrepancy in UK C. Process issue 1. Insufficient involvement with non-pharma consultees 2. NICE Patient Expert Report 2012	Comments noted. See responses below.
Myelodysplastic Syndromes UK/Leukaemia CARE (continued)	**A 1. Survival Benefit Issue** We were very surprised to read the NICE press release regarding the draft guidance: *"Commenting on the draft guidance,* ***Sir Andrew Dillon, NICE Chief Executive, said:*** *"The committee heard from clinical experts that lenalidomide is an effective therapy. However, the data provided by the company showed uncertainty about whether lenalidomide actually extended*	Comments noted. The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that, the convenience of a new oral treatment and reduction in the need for blood transfusions meant that lenalidomide offered a substantial step change in treatment. See section 4.14 of

Consultee	Comment	Response
	lives." Firstly - as mentioned in our original submission, and in the azacitidine STA, for such MDS patients , the quality of life gained through transfusion independence is of equal importance to survival – if not more important for some patients, due to their older age. As per our main submission and patient statements, lenalidomide is a drug that, through transfusion independence, drastically improves the quality of life of this group of del5q patients, who would otherwise be destined for supportive care only, and therefore be extremely limited in their daily activities. Therefore – placing the emphasis on survival, and not approving the drug because it may not increase survival, is not a valid argument in this group of patients. Secondly, the French randomised trial has shown a survival benefit for responders to the treatment. The trial shows a background transformation rate to AML of about 25% and less transformation and better survival for cytogenetic responders and those who become transfusion independent on lenalidomide. The topic of survival was previously discussed in the FAD, where the Committee seemed to agree on a survival benefit due to transfusion independence: FAD - http://www.nice.org.uk/nicemedia/live/13555/65538/65538.pdf *3.42 The manufacturer submitted the results of a systematic literature review to support its rationale that transfusion dependence is a prognostic factor for overall survival and rate of progression to AML. Sixteen of the 17 studies (mainly retrospective case series or registry populations, also one study describing the results of a randomised controlled trial and one post-hoc analysis of randomised controlled trial data – 5000 patients in total) meeting the inclusion criteria reported statistically significant associations between transfusion status and overall survival. This association was explained by:* • *transfusion dependence and anaemia leading to increased non-leukaemic death (particularly cardiac death)*	the FAD. The Committee noted the manufacturer's comments in response to consultation included an updated analysis of the MDS-004 trial data at 7 years, which continued to support a link between transfusion independence and overall survival. It concluded that it was plausible for lenalidomide to indirectly improve overall survival by improving transfusion independence. See section 4.5 of the FAD.

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	• *transfusion dependence and anaemia leading to increased risk of AML and leukaemic death* • *transfusion independence after dependency at baseline improving overall survival because of reduced complications from chronic anaemia.* • *The manufacturer also cited literature that examined the relationship between AML and both transfusion status and erythroid response, arguing that lenalidomide triggers programmed cell death in the deletion (5q) clone, and that the MDS-004 trial showed significant reductions in progression to AML for patients whose condition responded to lenalidomide* ***3.44 The ERG considered the additional information submitted by the manufacturer. It agreed that this information, combined with the results of the MDS-004 trial, suggested that it was reasonable to assume a 2-step relationship, first between lenalidomide response and transfusion independence, and then transfusion independence and overall survival.*** **3.46 and 4.6 of the FAD – "*Overall the Committee concluded that it was reasonable to assume a relationship between lenalidomide and transfusion independence, and transfusion independence and overall survival, although there remained uncertainty about the exact strength of the relationship and whether the relationship diminished over time.*"** We read the many sources of evidence in Table 1 in Evidence 03, which seem to have been overlooked by the committee? http://www.nice.org.uk/nicemedia/live/13555/67708/67708.pdf We also noted that NICE recognises and values the benefit of transfusion independence on QOL and potentially survival – in the following Guidance from April 2014: *National Institute for Health and Care Excellence- Appraisal consultation document – Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people having cancer treatment (including review of TA142) - Issue date: April 2014* ***Current practice***	Comment noted. The Committee recognised the need for treatments that would reduce blood transfusion dependence for people with MDS associated with an isolated deletion 5q cytogenetic abnormality (section 4.2 of the FAD). It also agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions meant that lenalidomide offered a substantial step change in treatment (section 4.14 of the FAD).

Consultee	Comment	Response
	4.3.1Clinical need of patients, including the availability of alternative treatments *The Committee heard from the patient expert that symptomatic anaemia is associated with fatigue and the inability to perform everyday tasks. It also heard from the clinical specialists that standard treatment for anaemia in people having cancer treatment includes blood transfusions, which could worsen quality of life and potentially shorten survival.* *The Committee concluded that people with anaemia who have cancer treatment need treatment options that potentially reduce the need for a blood transfusion and which improve quality of life.* *4.3.3 Estimate of the size of the clinical effectiveness including strength of supporting evidence* *The Committee concluded that ESAs were effective in increasing haemoglobin concentrations, improving haematological responses and reducing the need for blood transfusions.* *4.3.4 Based on the available evidence, the Committee concluded that it could not assume that ESA treatment either prolonged or shortened survival compared with treatments that did not include ESAs.* *4.3.5 The Committee concluded that the available evidence suggests that ESA treatment improves health-related quality of life compared with treatment without ESAs.* *4.3.9 Uncertainties around and plausibility of assumptions and inputs in the economic model. The Committee was concerned that the Assessment Group did not include disutilities associated with adverse reactions in the QALY calculation given that most adverse reactions occurred more frequently in the ESA arms. However, it recognised that there would be minimal effect on the incremental cost effectiveness ratios (ICERs) given that the adverse reactions in the study were rare.* *4.3.9 The Committee concluded that the QALY gain with ESAs may have been underestimated given that the potential benefits of ESAs associated*	Comment noted. The Committee considers those factors it believes are most appropriate to each appraisal (section 6.1.3 of the NICE Guide to the methods of technology appraisal). The Committee concluded that there was

Consultee	Comment	Response
	with avoiding blood transfusions and reducing the need for hospital visits were not captured in the QALY calculation. Reference to the fact that the drug may progress transformation to AML should no longer be relevant. The EMA having licensed the drug for del 5q as a single abnormality should be evidence enough that this topic is no longer an issue. A further paper, based on a subset of the MDS 004 trial also highlights the following results amongst the isolated del 5q patients, demonstrating longer overall survival in this group of patients: *Results: Rates of red blood cell-transfusion independence (RBCTI) ≥182 days were higher in the lenalidomide 10 mg (57.4%; P < 0.0001) and 5 mg (37.2%;P = 0.0001) groups versus placebo (2.2%). Cytogenetic response rates (major + minor responses) were 56.8% (P < 0.0001), 23.1% (P = 0.0299), and 0%, respectively. Two-year cumulative risk of acute myeloid leukaemia progression was 12.6%, 17.4%, and 16.7% in the lenalidomide 10 mg, 5 mg, and placebo groups, respectively. In a 6-month landmark analysis, overall survival was longer in lenalidomide-treated patients with RBC-TI ≥182 days* *Progression to AML by randomized treatment group is presented in Figure 2A. The estimated 2-year cumulative risk of progression to AML was 12.6% (95%CI: 5.4–27.7), 17.4% (95%CI: 8.7–33.3), and 16.7% (95%CI: 8.3–32.0) in the lenalidomide 10 mg, lenalidomide 5 mg, and placebo groups, respectively.* *The estimated 4-year cumulative risk of progression to AML was 30.6% (95%CI: 18.1–48.8), 35.4% (95%CI: 21.4–54.6), and 43.3% (95%CI: 27.6–63.1) in the lenalidomide 10 mg, lenalidomide 5 mg, and placebo groups, respectively.* ***Overall survival*** *Median OS was 4.0 years (95%CI: 2.5–NR), 3.5 years (95%CI: 1.7–4.8), and 2.9 years (95%CI: 2.2–4.2) in the lenalidomide 10 mg, lenalidomide 5*	considerable uncertainty over whether lenalidomide was associated with changes in the rates of AML progression for people with low or intermediate-1 risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. See section 4.6 of the FAD. Comments noted. The Committee noted that the manufacturer's comments in response to consultation included an updated analysis of these data at 7 years, which continued to support a link between transfusion independence and overall survival. Overall, the Committee concluded that it was plausible for lenalidomide to indirectly improve overall survival by improving transfusion independence (see section 4.5 of the FAD).

Consultee	Comment	Response
	mg, and placebo groups, respectively (Figure 3A). Of the 7 patients randomized to placebo who did not crossover to lenalidomide 5 mg, 6 (85.7%) died. In a 6-month landmark analysis, median OS was significantly longer in patients who achieved RBC-TI ≥182 days (5.7 years; 95%CI: 3.2–NR) compared with non-responders (2.7 years; 95%CI: 1.5–4.8; log-rank test P = 0.0072. *Median OS was similar in patients who achieved a major or minor cytogenetic response (4.3 years; 95%CI: 2.3–NR) compared with non-responders (3.7 years; 95%CI: 2.0–4.7; logrank test P = 0.4073; Figure 3C).* *In a study of untreated RBC transfusion-dependent patients with IPSS-defined Low- or Int-1-risk MDS and del(5q), median OS was approximately 3.7 years; 82% of the patients had isolated del(5q) (5). In the same study, RBC transfusion dependency was associated with shorter OS (HR 2.260; P = 0.001) in a Cox proportional hazards model of MDS patients with isolated del(5q). In the current analysis, median OS was significantly longer in patients who achieved RBC-TI ≥182 days compared with non-responders. Although OS by cytogenetic response was not significantly different between responders and non-responders, this lack of significance may have been due to the limited number of events and patients in this subset analysis.* **Extracts from "Outcomes in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with isolated deletion 5q treated with lenalidomide: a subset analysis from the MDS-004 study."** European Journal of Haematology, Article first published online: 9 JUN 2014, DOI: 10.1111/ejh.12380	

Consultee	Comment	Response
Myelodysplastic Syndromes UK/Leukaemia CARE (continued)	**2. PAS Scheme ACD 4.13** *4.13 The Committee questioned whether all the savings would be realised in practice for every patient because of the administration process involved. The Committee concluded that this added to the uncertainty of the cost reductions associated with the patient access scheme* Based on the official remit of PASLU, they are responsible for assessing the feasibility and administration burden of all patient access schemes for the NHS, not the committees, nor the ERG. We believe this topic should not have been raised. The PAS for lenalidomide was recommended as feasible, given the level of administration it requires. As per NICE documentation, PASLU is described as issuing robust advice: *"1.6 The process for advising whether implementing a patient access scheme is feasible in the NHS in England and Wales has been specifically designed to provide robust advice to the Department of Health. This advice will inform ministerial decisions on whether NICE should consider a patient access scheme as part of its technology appraisals programme.* *1.9 Most of the evidence that the PASLU needs to advise on whether a scheme is feasible is submitted by the manufacturer or sponsor of the technology. A review of the submitted information is produced by the PASLU, and if necessary the PASLU asks for further clarification (see 2.4.2). Further input is provided by the members of the independent Expert Panel and co-optees to the panel (see table 1). The PASLU asks for advice from within or outside NICE when necessary.* *Schemes should be clinically robust, clinically plausible, appropriate and monitorable (e.g. if it is a responder scheme, there must be a relatively straightforward way to measure a patient's clinical response). "* The description of the PASLU remit adds: *"The more systematic use of such schemes will need to be reviewed in light of experience. The timing of such a review will be jointly agreed but will be initiated not later than 2 years after the commencement of this agreement. "* We would welcome such a timed review, which should then show the drug in practice, further clinical benefits and the benefits for the NHS.	Comments noted. The Committee understood that patient access schemes are pricing agreements between the manufacturer and the Department of Health. The Committee acknowledged that there may be some uncertainty about the actual costs of lenalidomide paid in the NHS, but that it had no authority to assume a different cost than that agreed between the manufacturer and the Department of Health The Committee accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.

Consultee	Comment	Response
Myelodysplastic Syndromes UK /Leukaemia CARE (continued)	**3. Potential sub-group of patients for lenalidomide:** A portion of del5q patients are known (those with a P53 mutation) to have a sub-optimal response to lenalidomide. 18% of del5q patients have this mutation, based on paper referenced below. We suggest investigating further with MDS experts to check whether looking at only non P53 del5q patients would help reduce the cost-effectiveness "uncertainty" in this appraisal. Reference paper: J Clin Oncol. 2011 May 20;29(15):1971-9. doi: 10.1200/JCO.2010.31.8576. Epub 2011 Apr 25. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. Jädersten M1, Saft L, Smith A, Kulasekararaj A, Pomplun S, Göhring G, Hedlund A, Hast R, Schlegelberger B, Porwit A, Hellström-Lindberg E, Mufti GJ. "The probability of a complete cytogenetic response to lenalidomide was lower in mutated patients (0 of 7 v 12 of 24; P = .024). CONCLUSION: Importantly, mutations were present years before disease progression and were associated with an increased risk of leukemic evolution. Our findings indicate a previously unrecognized heterogeneity of the disease which may significantly affect clinical decision making." **4. Iron Chelation treatment (ACD 3.37)** Deferiprone was added to the cost calculations by the ERG. However this drug is not a licensed medication in this setting – this should have been checked with MDS experts before being added to the model.	Comments noted. Evidence for this potential subgroup was not available for the Committee to evaluate. However, the recommendation of lenalidomide as a cost-effective treatment for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate includes this subgroup of people. Comment noted.
Myelodysplastic Syndromes UK/Leukaemia	**[MDS UK and Leukaemia Care submitted additional patient statements which can be found in the evaluation report]**	

Consultee	Comment	Response
CARE (continued)		
Myelodysplastic Syndromes UK/Leukaemia CARE (continued)	**B** **2. Northern Ireland** Northern Ireland MP David McIlveen recently took part in a Northern Ireland Assembly presentation about access to treatment for rarer cancers. He called on ministers to address the issue of the severe lack of crucial drugs for cancer patients in this part of the country which does not benefit from the Cancer Drug Fund. We urge NICE and the committee to take these views into consideration. *Private Members' Business – Cancer Drugs: Funding* *Topic: The difficulties faced by patients obtaining funding for cancer drugs; concern about the varying policy positions throughout the UK and Ireland regarding the accessibility of cancer drugs; calls on the Minister of Health, Social Services and Public Safety to undertake a review into the practices in Northern Ireland to provide greater clarity for patients trying to obtain funding for cancer drugs.* *Comment extracted:* *"Mr McKinney: Thank you. I welcome the intervention. It is a point that I will expand on in just a moment.* *In England, as we are aware, a cancer drugs fund (CDF) is in operation that provides direct access for cancer sufferers to cancer drugs. In Scotland, just this month, the peer-approved clinical system has been put in place. That has replaced the IFR model and the clear inequalities in access that it was producing. In Wales, the All Wales Medicines Strategy Group is in place to appraise medicines before NICE. Consequently, that, too, improves access for cancer patients. However, a recent study by Bristol University uncovered that cancer sufferers in England are seven times more likely to receive the drug than those in Wales. There are varying journeys towards greater access to cancer drugs in the UK. We, however, are not yet at the starting line. When the SDLP has asked the Minister about that inequality, he has deflected it by bringing up the viability of the IFR process or even the issue of prescription charges or welfare reform.*	Comment noted. Lenalidomide is recommended as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Consultee	Comment	Response
	The Rarer Cancers Foundation and others have undertaken research about the cost of a CDF model here. It ranges between £5 million and £6 million. That is significantly less than the amounts needed in England, and it is feasible, we argue, if the Minister wants it to be. It is also important to note that, due to sophisticated molecular testing, improved diagnosis is available. Clinicians are available to accurately pinpoint which drug will work for a particular individual. So a cancer drugs fund model will cost more but will be much more refined and accurate than initially imagined." Northern Ireland and Wales are at an incredible disadvantage – as the Cancer Drug Fund is not available to those regions, therefore creating a post-code lottery – yet again. This issue also creates severe problems of cross regional referrals – causing a further and artificial strain on the NHS.	
Myelodysplastic Syndromes UK/Leukaemia CARE (continued)	This group of patients in this appraisal is extremely small – and therefore additional evidence from abroad must be considered to help reduce the uncertainty the Committee still struggles with. We strongly request that the Committee engages with as many MDS experts as possible, in order to gather further clinical evidence, as opposed to requesting additional data from the manufacturer. To date, only one MDS expert was consulted internally at NICE, which we insist is neither satisfactory, nor objective or conclusive. We request specifically that the 31.9% survival estimate at 26 cycles of treatment be validated by several experts in the UK and abroad. We strongly believe this would assist in reducing uncertainty. Previous NICE appraisals benefitted from the "small population criterion" as in the HTA below. We believe that lenalidomide fits in with this particular concept. http://publications.nice.org.uk/pemetrexed-maintenance-treatment-following-induction-therapy-with-pemetrexed-and-cisplatin-for-ta309/consideration-of-the-evidence	Comments noted. The Committee agreed that, because the proportion of people remaining on treatment after 26 cycles in clinical practice was uncertain, so were the potential cost savings from the patient access scheme. The Committee accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD).

Consultee	Comment	Response
	4.21 The Committee discussed the small patient population criterion. It heard from NICE that, for treatments for small groups of patients, higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product if the licensed indications only apply to a small potentially eligible patient population. It further heard that the case for reduced cost effectiveness weakens as the potential total population for a product increases. Therefore, taking into account the cumulative population covered by all the indications in the marketing authorisation needs to be considered. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation. **4. Scotland and SMC appraisal** The SMC was satisfied with the data provided for their appraisal of this same drug and was able to approve the drug for Scotland. The process and work by this HTA group was just as rigorous as NICE. Following the approval in Scotland, patients are once again facing a post-code lottery. This is again increasing issues of regional cross referrals.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Evidence Review Group's economic analysis and the manufacturer's submission. It also carefully considered the comments received from consultees and commentators in response to the ACD.
Myelodysplastic Syndromes UK/Leukaemia CARE (continued)	**C.** **1. Insufficient involvement with Patient group consultees.** Since the publication of the FAD, we requested more ample involvement, in order to assist with the validation of clinical data. Despite regular communication, this did not take place and we as patient groups, nor the clinical expert groups were fully informed about the additional data requested from the manufacturer. This unfortunately also reflects the experience gathered in the recent NICE Patient Expert Report 2012, which was released recently – extracts below. We would again urge NICE and committees to take this opportunity to engage more fully with patient group consultees at every stage of the appraisal. **2. Report – NICE Patient Expert Survey**	Comments noted. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness and it heard about the benefits of lenalidomide from patient and professional groups during consultation. It agreed that, the convenience of a new oral treatment and reduction in the need for blood transfusions meant that lenalidomide offered a substantial step change in treatment (see section 4.14 of the FAD).

Consultee	Comment	Response
	The results of a NICE survey amongst patient experts conducted in 2012 shows that unfortunately, two years later, NICE committees have still not taken up the opportunity to work more closely with patient experts, and use their knowledge and experience to improve and assist in the appraisals. We find ourselves facing similar issues in this lenalidomide appraisal. *National Institute for Health and Care Excellence - Technology Appraisal Patient Expert Survey 2012 Report. By Lizzie Amis and Heidi Livingstone - Public Involvement Programme* *Experiences during the committee meeting - overall experience* *"Not only did the patient experts find the slide presentation more difficult to understand, but also only just under half the patient experts (48%) thought that the slides addressed the key patient issues, with over a third (33%) saying that they thought they were not addressed.* *"The slide presentation did not properly address patient needs and the reasons why one of the technologies appraised was more beneficial to some patients than others. This had to be explained by the clinical experts."* *"There was patient experience as far as goes side effects etc. however the patient experience is far more than this. My overriding feeling with NICE TAs is that it is hard science driven, and the wider patient issues have little consideration/value to the determination."* *"The cost effectiveness Committee 'lead team' member addressed issues that could not be described as 'key patient issues' but were rather (broadly) NHS resources issues. There are generally a large number of slides in his presentation* *Only 65% of patient experts were aware that there is a lay member of the committee responsible for that particular appraisal topic.* *The comments about the lay members and the lay lead role vary and show that there could be an improvement in awareness of and understanding of the lay members of the committee and the lay lead role.* *There is considerable room for improvement; only about 40% said that they*	

Consultee	Comment	Response
	understood the slide presentations and could follow and participate in the discussions. Just under half thought that the patient issues were represented in the slides. *There were comments about the patients presence being 'tokenistic' and that the patient experience has little to do with the committee's overall determination* *Although 65% knew that there was a lead lay member responsible for their topic, there was a lack of clarity about what their role is.* *Other patient experts thought that although some of the key issues were addressed some still were not and point out what they see as the flaws regarding NICE's methodology for including patient issues.* *"Obviously some key patient issues were addressed but not all. I fail to understand how NICE can be a partner in an initiative like the Technology Strategy Board (TSB) 'Stratified Medicine Innovation Platform' which accepts that randomised clinical trial (RCT) evidence is not exhaustive, although not without value, whilst simultaneously elevating RCT evidence via inclusion/exclusion criteria, to be the sole clinical evidence on which economic models are built. The key patient issue is that clinically speaking not all patients, even though they have the same diagnosis, are the same. The modelling effectively shuts out evidence that might offer redress to that relied upon."* ***What is most important to patient experts?*** *The most important issues for patients are:* *1. Being able to raise relevant issues at the committee meeting* *2. Feeling that their contribution made a difference* ***Feeling that their contribution made a difference*** *This is one of the top two issues of important to patient experts and thus another key area for improvement. Although the majority of the patient experts felt their contribution made a difference, there were issues of: a feeling of tokenism; the organisational statement being more relevant than the patient expert presence; feeling that not all patient issues were addressed; feeling that patient issues and evidence are not viewed equally*	The Committee understood that patient access schemes are pricing agreements between the manufacturer and the Department of Health. The Committee acknowledged that there may be some uncertainty about the actual costs of lenalidomide paid in the NHS, but that it had no authority to assume a different cost than that agreed between the manufacturer and the Department of Health. The Committee accepted that a commitment from the manufacturer to publish data on the

Consultee	Comment	Response
	with the RCT evidence and the health economics. **Final comments** We firmly believe there is a possibility to reduce the uncertainty in this STA by involving all stake holders and consultees, given the issues we raised in our comments, and the information we provided – if used by the committee. We urge NICE to pursue this consultation further to come to an acceptable outcome in order to make the drug available – and therefore remove the current unacceptable regional discrepancy. We remain at the Committee's disposal for any additional information.	proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.
Royal College of Pathologists and British Committee for Standards in Haematology	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, notably Jehovah's Witnesses, which as far as I can see have not been considered as a patient group in this consultation. For such individuals with 5q- syndrome who are refractory to erythropoietin, the decision to refuse blood products leaves them with little alternative therapeutic options. The use of Lenalidomide in this situation would be justifiable both medically and morally and, if so, then withholding Lenalidomide on economic grounds from other patient groups could potentially be considered discriminatory in a court of law.	Comment noted. The Committee considered the potential for discrimination to individuals who cannot receive blood products on religious groups, and 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. The Committee concluded that lenalidomide could be recommended for treating MDS associated with an isolated deletion 5q cytogenetic abnormality as a cost-effective use of NHS resources and therefore it did not need to amend any of its recommendations for the group of patients unable to receive blood transfusions.

Consultee	Comment	Response
Royal College of Pathologists and British Committee for Standards in Haematology (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 a highly effective therapy and yet the few patients with 5q- syndrome are clearly being treated differently to the many patients with myeloma for whom Lenalidomide is offered in the United Kingdom as third line treatment. 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. This is particularly unfair given the orphan disease status of 5q- syndrome, which is not clearly apparent in the Committees considerations.	Comment noted. The Committee considered all the evidence submitted specific to the decision problem specific for this therapeutic indication. This included evidence related to clinical and cost effectiveness that was from specific clinical trials, patient and clinical experts, the Evidence Review Group's economic analysis and the manufacturer's submission. The Committee has recommended lenalidomide as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.
Royal College of Pathologists and British Committee for Standards in Haematology (continued)	3. The Scottish Medical Consortium has recently approved an identical Patient Access Scheme that now operates in Scotland. This decision clearly challenges the conclusion of NICE not to grant funding to Lenalidomide in this clinical setting and creates a potentially serious problem of regional geographic inequalities within the NHS.	Comment noted. The Committee has recommended lenalidomide as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Consultee	Comment	Response
Royal College of Pathologists and British Committee for Standards in Haematology (continued)	4. The Committee question the estimate of patients continuing for more than 26 months on Lenalidomide at 27% at which point the funding of the treatment by the NHS becomes cost effective. In my professional opinion, the company Celgene has provided extremely clear evidence that this is a very reasonable (and in some regard conservative) estimate that has been arrived at using published real world data from a Spanish study. Moreover, the Scottish Medical Consortium has accepted the advice of its own consultants that this estimate is indeed representative of the clinical practice population.	Comment noted. The Committee accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.
Royal College of Pathologists and British Committee for Standards in Haematology (continued)	5. The Committee appear to question the link between transfusion independence and overall survival in 5q- syndrome which is clearly well established and provides a good argument in favour of Lenalidomide cost effectiveness even without consideration of the enormous improvements in quality of life that are also seen in responsive patients.	Comment noted. The Committee concluded that it was plausible for lenalidomide to indirectly improve overall survival by improving transfusion independence. See section 4.5 of the FAD.
Royal College of Pathologists and British Committee for Standards in Haematology (continued)	6. The current access to Lenalidomide in 5q-syndrome via the National Cancer Drugs Fund complicates and largely obviates the current NICE Appraisal Consultation Document. In light of this, a cost-sharing Patient Access Scheme, as proposed by the marketing company Celgene, appears to be a pragmatic way forward in terms of making this treatment available to eligible patients within its current marketing authorisation and along similarly lines to Lenalidomide funding in relapsed multiple myeloma. The Committee has also disregarded the fact that, according to the company's own TCS database, a significant number of patients in the UK are currently receiving Lenalidomide, some up to as many as 70 cycles of treatment, that is presently being funded by the NHS but who would have this cost covered by Celgene were the proposed Patient Access Scheme to be adopted.	Comment noted. The Committee has recommended lenalidomide as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The Committee accepted that a commitment from the manufacturer to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS. See sections 4.11 and 4.13 of the FAD.

Comments received from clinical specialists and patient experts

See above

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1 (Appraisal Committee's preliminary recommendations)	As Consultant Haematologists specialising in myelodysplasia and other myeloid malignancies and as representatives of the UK MDS Forum, a charity representing expert opinion and funding education and research among scientists and physicians with an interest in myelodysplasia, we wish to express our concern at the recent NICE ruling on lenalidomide. We are of the opinion that the published data from the MDS-004 and other studies strongly supports the use of lenalidomide as first line treatment in patients with transfusion dependent myelodysplasia associated with the isolated 5q deletion. More than two-thirds of patients will have a significant, meaningful improvement in transfusion requirements with an unprecedented improvement in quality of life. Patients are protected from adverse complications of blood transfusion, including infection, alloimmunisation and iron loading, and so avoid costs associated with these conditions.	The Committee has recommended lenalidomide as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The Committee agreed that if the manufacturer committed to collect data to address the uncertainties of the assumptions used in the economic model relating to the proportion of people remaining on treatment, the Committee could be assured that lenalidomide was a cost-effective use of NHS resources. See sections 4.11 and 4.13 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	2 (The technology)	Primarily we are concerned that transfusion dependence and iron loading are both associated with a shortened survival outcome in patents with myelodysplasia and that this is alleviated by using lenalidomide. Patients responding to lenalidomide can have excess iron removed through venesection which is much cheaper and much more effective than subcutaneous or oral iron chelation therapy. When started sufficiently early in the patient?s journey, significant iron loading may be avoided completely. Concern has been raised regarding the number of patients reaching 26 weeks therapy. It is my view that sufficient numbers reach this end point as to merit an interim ruling by NICE that allows patients to be treated in a national surveillance database with a review of these data after a five year follow up, after which a further ruling could be made as to cost effectiveness. We would urge NICE to reconsider the recent interim ruling and allow patients with this malignant and crippling orphan condition access to a life changing and disease altering medication which has been shown, in randomised studies, to impact favourable on transfusion need, quality of life, and survival outcomes.	The Committee has recommended lenalidomide as an option within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The Committee agreed that if the manufacturer committed to collect data to address the uncertainties of the assumptions used in the economic model relating to the proportion of people remaining on treatment, the Committee could be assured that lenalidomide was a cost-effective use of NHS resources. See sections 4.11 and 4.13 of the FAD.
	7 (Related NICE guidance)	With careful national surveillance, review could be undertaken between three and five years after commencement of drug availability to ascertain number of patients remaining on drug.	The Committee agreed that if the manufacturer committed to collect data to address the uncertainties of the assumptions used in the economic model relating to the proportion of people remaining on treatment, the Committee could be assured that lenalidomide was a cost-effective use of NHS resources. See sections 4.11 and 4.13 of the FAD.