NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD) issued January 2009

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 patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

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	We believe that the appraisal considered all of the relevant evidence for the use of lenalidomide in previously treated multiple myeloma that was available. Celgene would like to endorse the Committee's decision that the appraisal of lenalidomide fulfilled the criteria for supplementary advice as a life-extending therapy. We wish to provide further clarity to the Committee's decision given that Celgene was unable to comment on the 'end of life criteria' in our response to the first ACD in October 2008. The criteria and our supporting evidence are set out below: *1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months;* From a historical perspective, overall survival in patients receiving one prior therapy for multiple myeloma has been estimated at a median of 14.4 months (1.2 years) from a retrospective analysis of UK Myeloma trials IV, V, VI and VII between 1980 and 1997 (n = 2,528) . Thus, overall survival in patients who have received at least one prior treatment is very likely shorter than 24 months. The findings in the control arm of the MM-009/010 trials are confounded due to the permitted cross-over from dexamethasone to lenalidomide. The observed overall survival for patients treated with dexamethasone reached 31 months (NICE submission pages 84-85), but 47% of patients had crossed over to lenalidomide following	Comments noted. See FAD sections 4.17 to 4.19 for the Appraisal Committee's considerations of the Institute's supplementary advice to Appraisal Committees on end of life treatments with regard to this appraisal.

Consultee	Comment	Response
	disease progression or study unblinding. Further analyses of these Medical Research Council (MRC) data revealed that median overall survival for patients with one prior therapy was 16.1 months and for at least two prior therapies was 9.2 months (NICE submission pages 114-115 and Appendix 8). Even when adjusting these MRC overall survival data for the characteristics of patients treated with dexamethasone from MM-009/010 the survival remained well below 24 months for both one prior therapy (19.5 months) and at least two prior therapies (11.6 months) (NICE submission pages 114-115 and Appendix 8). Given the position of lenalidomide and dexamethasone following at least two prior therapies, it is without doubt that the expected survival (life expectancy) is less than 24 months with current standard treatment. *2. There is sufficient evidence that the treatment offers an extension to life, normally of at least an addition 3 months, compared to current NHS treatment;* The pivotal MM-009/010 studies demonstrated that the median overall survival in patients who have received at least one prior therapy was improved by more than 3 months (lenalidomide/dexamethasone vs. dexamethasone) even without adjusting for the cross-over to treatment with lenalidomide following disease progression or study unblinding.	

Consultee	Comment	Response
	In the updated MM-009/010 data cut in January 2007 the median overall survival with lenalidomide/dexamethasone was 35 months (149.7 weeks) compared with 31 months (133.3 weeks) in the dexamethasone arm (NICE submission pages 84-85). Further analysis of the MM-009/010 overall survival data by number of prior therapies demonstrates that the extension of life remained substantially in excess of 3 months regardless of number of prior therapies. For patients with one prior therapy the median overall survival with lenalidomide/dexamethasone was 39 months (169.1 weeks) compared with 33.5 months (145.4 weeks) in the dexamethasone arm (NICE submission pages 87). For patients with at least two prior therapies the median overall survival with lenalidomide/dexamethasone was 33 months (144.0 weeks) compared with 27 months (118.0 weeks) in the dexamethasone arm (NICE submission pages 87). Importantly, following adjustment for the cross-over effect the extended survival was 19.5 months (39 months – 19.5 months) in patients who had received one prior therapy and 21.4 months (33 months – 11.6 months) in patients who had received at least two prior therapies (NICE submission page 87 and pages 114-115). Celgene believes that this evidence categorically demonstrates that Revlimid meets the criteria for extending life.	

Consultee	Comment	Response
	3. No alternative treatment with comparable benefits is available through NHS; Celgene would like to endorse the Committee's decision that there are no alternative treatments with comparable benefits available through the NHS. Bortezomib (Velcade) is currently recommended by NICE for patients who have received one prior therapy only and by definition is not widely available through the NHS for patients who have received at least two prior therapies as it was deemed unlikely to be cost-effective in the completed technology appraisal (TA129). Thalidomide, as per the Committee's decision comments, is only licensed as a first line treatment and is not licensed in previously treated multiple myeloma. Furthermore, there is no evidence to support the effectiveness (or comparable benefit) of thalidomide in patients who have been treated with two or more prior therapies. Dexamethasone or other conventional therapies are available through the NHS, but they do not have proven comparable benefits to lenalidomide. Indeed, dexamethasone was proven in studies MM-009/010 to be inferior to lenalidomide/dexamethasone. Thus, Celgene believes that no alternative treatments are available through the NHS with	

Consultee	Comment	Response
	comparable benefits to lenalidomide. *4. The treatment is licensed, or otherwise indicated, for small patient populations.* Lenalidomide has been granted orphan status by the Committee for Orphan Medicinal Products, on the basis that multiple myeloma is not only rare (occurring in fewer than 5 in 10,000 persons in the European Union), but is both life threatening and debilitating, in addition to representing a disease with significant unmet medical need. Treatment of multiple myeloma with lenalidomide was entered in the Community Register of Orphan Medicinal Products under the number EU/3/03/177 on 12 December 2003. We estimated the number of patients in the UK who have had 2 prior therapies and therefore are eligible for lenalidomide is approximately 2,100.	
	We agree that the summaries in the ACD are reasonable interpretations of our submissions and the ERG analyses. However, we maintain that the use of median in the survival analysis is a correct analysis based on our scientific reasoning in previous communications. We are pleased that the Committee noted in Section 4.15 that the 'choice between using mean or median survival was a scientific judgment' and, although calibration to the mean was determined to be the reviewer's preferred approach in this case, we respectfully withdraw from further discussions on this methodology. We agree that, using the ERG approach and the	Comments noted.

Consultee	Comment	Response
	second analysis we submitted, the ICERS are £43,800 (1.81 life years gained and 1.24 QALYs gained) for two or more prior therapies and £41,300 (1.71 life years gained and 1.15 QALYs gained) for prior therapies including thalidomide (Section 3.22).	
	We agree with the Committee's recommendations based upon the submitted data, the nature of multiple myeloma and the value placed on the benefits of lenalidomide by patients, their carers and clinical experts. We strongly concur with the Committee's consideration that the extended life years in this patient population might be given full quality weight in determining the ICER. The Committee commented that 'the magnitude of the additional weight that would need to be assigned to the original QALY benefit for the cost effectiveness of lenalidomide to fall within the currently applied ICER threshold range was acceptable.' We are pleased that the Committee has made this consideration for the option to use lenalidomide for the treatment of multiple myeloma patients who have received two or more prior therapies. The *quantitative exploration* provided by the review team adopts the van Agthoven et al. estimation of a health utility value of 0.81 for the multiple myeloma patients alive and 'healthy' for this population and we concur with this approach as having a basis in the published literature.	Comments noted.
	We do not know of any equality related issues not addressed in the ACD.	Comment noted.
PCT	In summary, we do not support the ACD provisional recommendations as we believe that	Comments noted.

Consultee	Comment	Response
	the economic case has not been demonstrated. Yes, we think that you have considered all the relevant evidence that is available in the public domain. Yes, we think that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. No, we do not concur with the provisional recommendations of the Committee and we do not think that they constitute a suitable basis for the preparation of guidance to the NHS. No, we are not aware of any equality issues that need special consideration.	
	1 In the event that NICE approves this drug, it should provide a clear definition of who should be eligible for this drug, e.g. does NICE propose the use of lenalidomide only after receiving two treatments or as 3rd, 4th, 5th etc line of treatment. Furthermore, it would also be helpful to provide a definition of what constitutes a course of treatment (paragraph 1.1). 2 NICE should make clear whether VAT has been incorporated in its cost effectiveness assessments (paragraph 2.3).	The recommendations in the FAD (1.1) state that lenalidomide can be used as a treatment option for people who have had two or more prior therapies. The trials included people who had at least one previous therapy and included people whose disease had relapsed or was refractory. Treatment in the clinical trials was continued until disease progression or the occurrence of unacceptable adverse effects (see FAD 2.2), and this is the approach taken in clinical practice. Cost is ex-VAT as specified in 2.3

Consultee	Comment	Response
	3 It is not clear why NICE has not included decrements for adverse effects (paragraph 3.13).	Section 3.13 of the FAD describes the economic analysis in the manufacturer's submission. The effect of adding utility decrements for adverse events was explored in a sensitivity analysis (see FAD 3.19, 4.13 and 4.15).
	4 We agree that the preferable method of calculation is using the means and not the medians. Although the former is not perfect, it is a much better approach giving more plausible results (paragraphs 3.16, 4.10, and 4.15).	Comment noted.
	5 It is not clear how the incremental life-year gain, the incremental QALY gain and the ICERs were derived (paragraphs 3.20 and 3.22). It will be helpful to make these calculations more explicit.	The incremental QALY and LYG are derived as outputs of the economic model submitted by the manufacturer and critiqued by the Evidence Review Group. The evidence is summarised in section 3 of the FAD. For further details, please see the Manufacturer's Submission, Evidence Review Group report and the clarification request and response. The ICERs in 3.20 and 3.22 are the ratios of incremental costs to incremental QALYs.
	6 It is not clear how NICE derived the figures of 17% and 11% of patients who would benefit from a capping scheme. Is this based on NHS everyday experience or modelling (based on what evidence?) (paragraph 3.21).	These proportions are results from the economic model as stated in the FAD section 3.21.
	7 It is important that NICE clarifies the optimal sequence of agents in treating multiple myeloma (paragraph 4.2).	The remit of the appraisal is to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications for multiple myeloma. Specifying the optimal sequence of agents to treat multiple myeloma would be a broader than the remit of the appraisal. This guidance will be considered for review together with technology appraisal 129 (see FAD 7.2).

Consultee	Comment	Response
	8 In our view, bortezomib and thalidomide are both used enough in everyday clinical practice to justify being used as comparators and as a result dexamethasone is not the best comparator (paragraphs 4.3 and 4.4).	Bortezomib is not recommended by NICE for second and subsequent relapses. Thalidomide is not licensed for this indication and an application for a licence in relapsed or refractory multiple myeloma was withdrawn. The Committee were aware that it is a treatment option that is used within the NHS, however the extent of its use within the NHS is not known. The Committee also noted a statement from the manufacturer that there is a lack of evidence for its efficacy for this indication, in particular after failure of two or more therapies. The Committee accepted that in people who have received two or more prior therapies, high-dose dexamethasone was a reasonable comparator for lenalidomide. (FAD 4.4).
	9 We agree that ICERs per QALY are likely to be higher (paragraphs 4.12 and 4.13).	Comment noted
	10 We agree with NICE conclusion that use of lenalidomide for the treatment of multiple myeloma in people who had received only one prior therapy is not cost effective (paragraph 4.14).	Comment noted.
	11 It is not clear the logic behind the argument in paragraph 4.19.	This paragraph takes in to account the Institute's supplementary advice to Appraisal Committees on end of life treatments. The advice states that the Appraisal Committee will consider the magnitude of additional weight that would need to be assigned to the QALY benefits in groups of patients with terminal illnesses for the cost-effectiveness of the technology to fall within the current threshold range. The Committee considered that the extra weight that would need to be placed on QALYs gained for people with multiple myeloma who have had two or more prior therapies in order for lenalidomide to be considered a cost effective use of NHS resources was acceptable.

Consultee	Comment	Response
	Furthermore, we would like to reiterate the comments we made during the first consultation appraisal:	
	12 We agree that multiple myeloma is an incurable disease and that lenalidomide is a clinically effective medicine for this condition.	Comment noted.
	13 Lenalidomide has a considerable side effect profile that is however less toxic compared to thalidomide. However, the current knowledge is based on a small cohort of patients recruited for the lenalidomide studies.	Comment noted. See FAD section 4.7 for the Appraisal Committee's considerations of adverse events.
	14 We are also concerned that if a patient is started on lenalidomide, it is unclear for how long it should be administered. It would also be helpful if more clarity was provided on the preferred sequence of treatments, the length of treatment, and to define progression and clinical response (e.g. defined objective outcome measures and exit criteria).	In the clinical trials, lenalidomide was administered until disease progression or the occurrence of unacceptable adverse effects and this is the case in clinical practice. The appraisal does not make recommendations for the sequencing of treatments. This guidance will be considered for review together with Technology Appraisal 129 (see FAD 7.2). Disease progression is determined by clinicians and is usually based on criteria developed by the EBMT and/or the International Uniform Response Criteria. (FAD 3.2)
	15 We think that the RCTs of lenalidomide do not have appropriate comparators such as thalidomide or bortezomib and that the high degree of crossover (47%) from control to the active arm makes very difficult the quantification of the likely degree of benefit. We are concerned that these questions are not likely to be addressed.	Comment noted. See sections 4.2 to 4.7 which summarise the Appraisal Committee's considerations regarding relevant comparators and clinical evidence of the effectiveness of lenalidomide compared with them.

Consultee	Comment	Response
	16 Thromboprophylaxis (such as low molecular weight heparin or warfarin) is recommended in patients receiving lenalidomide, who have additional risks for thrombosis.	Clinical expert opinion submitted to the Committee was that the usual DVT prophylaxis in patients with relapse multiple myeloma was with aspirin. Sensitivity analysis for the costs of prophylaxis found the ICERs not to be sensitive to this assumption (3.20).
	17 Sandwell PCT has received individual funding requests for lenalidomide in multiple myeloma and after appraising the published literature/evidence, we came to the conclusion that lenalidomide within the cancer treatments, is relatively effective and a promising therapy, but when the balance of costs and health benefits were considered, it was thought not to be cost effective in its current pricing and not affordable, given that this is a relatively common condition. The opportunity costs are considerable for a health organization that has to fund health care across the board for its whole population. We would be happy to consider funding if the cost was reduced.	The average cost of lenalidomide for patients who have had two or more prior therapies has been decreased through the patient access scheme. Having considered the evidence and issues set out in the FAD, the Appraisal Committee concluded that lenalidomide would be a cost effective use of NHS resources in the specified subgroup of people who have had two or more prior therapies and under the conditions of the of the patient access scheme.
	Finally, we would like to take the opportunity to reiterate our disappointment with the consultation process so far. We are aware that our comments submitted for the first appraisal document of lenalidomide were reported in the large (244 pages) appendix document. However, on the Committee day, on 6th January 2009, there was no acknowledgement or discussion of our comments. We have responded to this consultation because we think that providing a	The Committee receive and consider all comments but the focus of discussion will depend on factors such as the extent to which the issues raised in the comments were already discussed at previous meetings, and on how pivotal the Appraisal Committee considers them to decision making. All comments are seen by committee members and are available on the website. For comments on the first ACD issued in October 2008 see http://www.nice.org.uk/guidance/index.jsp?action=folder&o=43007. All comments were considered in further detail at the second Committee meeting.

Consultee	Comment	Response
	PCT perspective is desirable and useful to NICE that has to make at times very difficult decisions. On the day, it appeared that the only comments that were considered and debated were the ones from Celgene and the ERG.	
	In our opinion, ultimately to fund or not to fund a drug is a policy decision that can only be helped and supported by the health economic analysis and not substituted by it. So, however important that it may be, whether we should consider the median or the mean for the control group, this detail can not and should not be the deciding factor whether NICE agrees to fund lenalidomide.	Comment noted. The remit of the appraisal is to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications for multiple myeloma. The recommendations are based on appraisal of the evidence, and a major factor in the economic evidence was the issue of whether survival modelling was calibrated to the mean or median of underlying data.
	As we have already noted in our submission to the NICE consultation on 'Appraising end of life medicines', this appraisal is an example of the consequences of the application of the new rules. The proposed treatment offers poor value for money and is not affordable within the current funding streams. It is likely to contribute to the distortion of priorities across the spectrum of health and health care and to incur opportunity costs to Sandwell Primary Care Trust. In the absence of additional funding streams, this will be to the detriment of funding for other end of life	Comment noted. The Appraisal Committee's considerations of the Institute's supplementary advice to Appraisal Committees on end of life treatments are summarised in sections 4.17 to 4.19 of the FAD.

Consultee	Comment	Response
	care. For Sandwell PCT, a greater priority is for example the development of an NHS hospice to meet the needs of our population. If this proposal is approved, it will make it much harder to decline funding for any 'rule of rescue' end of life treatment of marginal benefit. It will also affect our ability to make reasonable judgments in assessing the value of other new technologies not appraised by NICE and effectively open the door to the wide use of poor value treatments.	Comment noted.
BSH/UKMF	Yes. Our organisations, the British Society for Haematology (BSH) and the UK Myeloma Forum, (UKMF) are very pleased that the Committee, having considered the evidence from the ERG, taken into account the price capping scheme offered by the manufacturer, and agreeing that Lenalidomide for myeloma fulfils the criteria of a life extending medicine, has recommended that Lenalidomide and dexamethasone be made available for patients with myeloma at second relapse and beyond. As previously stated, we consider Lenalidomide to be a well tolerated, effective drug in patients with relapsed myeloma and we are in no doubt as to the importance of and the positive impact the Committee's decision will have on the lives of people suffering with this disease.	Comments noted.
	We believe the Committee, after rigorous examination of the all evidence has made the correct decision in recommending that Lenalidomide be made available.	Comments noted.

Consultee	Comment	Response
	We recognise and appreciate that the Committee has listened and agreed to feedback from stakeholders on a number of specific issues. However, we note that it still expressed some doubts about the costs and disutilities for the adverse effects and anti-thrombosis prophylaxis for Lenalidomide. We take this opportunity to further reassure the Committee that these doubts are unjustified as increasing clinical experience demonstrates to us that side-effects, such as they are, are mostly experienced early in the treatment course and lessen over time. They are very easily and cheaply managed and have proved in reality not to be the issue and challenge as they may have first appeared from the data which emerged from the trials. We are delighted that the desperate need of patients facing certain death has been acknowledged by the Government and that NICE and the Committee have acted swiftly in implementing the new advice concerning end of life medicines and agreed that Lenalidomide for myeloma at second relapse and beyond meets all the criteria for the new advice to be applied.	
	We do believe the recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. In particular we feel that the capping scheme is simple, will be easy to implement and represents a good deal for the NHS. We understand it is necessary to ensure that NHS resources are	Comments noted. Also, please note that the Appraisal Committee considered that rigorous data collection is needed on the life-extending benefits of lenalidomide when used in people who have had two or more prior therapies (see FAD section 6.1).

Consultee	Comment	Response
	used cost effectively and we seek to reassure the Committee that through our professional groups via guidelines, teaching and training, we will make every effort to ensure that the guidance is implemented responsibly and delivers maximum benefit to patients and the NHS.	
	We are not aware of any equality related issues that need special consideration not covered in the ACD	Comment noted
Macmillan	We are delighted that the recently issued second ACD on the use of lenalidomide for the treatment of multiple myeloma is positive for people who have received two or more prior therapies. This is a small patient group and we feel that this second Appraisal Consultation Document reflects their needs. We do however remain concerned that as stated in point 4.2 of the ACD "the optimal sequence of agents to use is as yet unclear and depends on several factors, including a person's treatment history, co-morbidities and disease characteristics." The Committee found lenalidomide to be cost-ineffective in patients at first relapse. However, we would urge the Committee to reconsider this in relation to the small group of patients for whom bortezomib is not suitable at first relapse. We are pleased that the manufacturer has offered a price-capping scheme for lenalidomide to ensure that this important treatment is more affordable to the NHS.	Comments noted This subgroup was considered by the Committee and lenalidomide was found not to be cost effective (FAD 4.11). No further evidence for this subgroup was submitted by the sponsor and the Appraisal Committee's conclusions on this did not change after the second Committee meeting.
Myeloma UK	We are satisfied that all evidence has been taken	Comments noted.

Consultee	Comment	Response
	into account and we are happy with the outcome. We are pleased that the price capping scheme offered by the manufacturer and the application of the supplementary end of life guidance means that myeloma patients who have received two or more prior therapies and are suitable for lenalidomide will now get access to this clinically effective treatment. Whilst we are pleased that this draft recommendation is positive, we remain concerned and surprised about the magnitude of difference between the manufacturer's base case QALY and the ERG's, and that there was such a marked divergence of opinion as to whether mean or median should have been used in the economic model. To reiterate a point made in our response to the negative ACD: given the increasing frequency of crossover trials and the likely consequences that crossover has on the validity of data, we recommend the Institute establishes a standard method to assess treatments which are penalised by the current appraisal process for being the focus of trials unblinded early because of their superior clinical effectiveness.	See FAD sections 4.9 to 4.11 describing the Appraisal Committee's considerations regarding cross-over and survival modelling. The Institute regularly reviews its processes and methodology. The Guide to the Methods of Technology Appraisal was recently updated following public consultation. Models are required for most appraisals and situations when modelling is likely to be required include those where all the relevant evidence is not contained in a single trial and the long-term costs and benefits of the technologies extend beyond the trial follow up. Such situations include those such as in this appraisal where cross over needs to be adjusted for. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. When the impact of treatment beyond clinical trials is uncertain, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects should be presented. For further details, please see the Guide to the Methods of Technology Appraisal http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	We feel the recommendation is a fair reflection of the evidence and represents a good deal for both patients and the NHS. We applaud the willingness and commitment of the Institute, the Department of Health and the manufacturer to making lenalidomide available on	Comments noted

Consultee	Comment	Response
	the NHS and for creating an innovative solution to ensure that this important drug can be accessed by patients.	
	As the recommendation stands, we consider it a sound and suitable basis for guidance to the NHS. We urge the Institute to convert this draft guidance into final guidance as soon as possible.	Comment noted
	We do not know of any equality related issues not addressed in the ACD.	Comment noted
Rarer Cancers Forum	Rarer Cancers Forum welcomes and warmly endorses the Appraisal Committee's preliminary recommendations. We sincerely hope that the final outcome will be a positive final appraisal determination (FAD). We totally agree with the Committee that the "population and the technology of interest meet the criteria for accepting that this is an appraisal of a life extending, end-of-life treatment and that the evidence presented for this consideration was supported by robust data". Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? We agree. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? They are sound and are most definitely an	Comments noted. See FAD sections 4.17 to 4.19. Also, please note that the Appraisal Committee considered that rigorous data collection is needed on the life-extending benefits of lenalidomide when used in people who have had two or more prior therapies (see FAD section 6.1).

Consultee	Comment	Response
	admirable basis for the preparation of guidance to the NHS which will have an enormously beneficial impact on the lives of patients and their families. Are there any equality related issues that need special consideration that are not covered in the ACD? No.	
RCP	Our organisation believes that the Committee has considered all the relevant evidence in coming to its conclusion that lenalidomide for myeloma fulfils the criteria of a life extending medicine, and recommending that Lenalidomide and dexamethasone is clinically effective and should be made available for patients with relapsed/refractory myeloma. Lenalidomide has been shown in a number of studies to be well tolerated and effective in the relapsed/refractory setting and we are in no doubt as to the impact the Committee's decision will have on the lives of patients with this disease, their family and carers.	Comments noted
	We believe the Committee, has made the appropriate decision in balancing the cost: benefits of this new technology in recommending that Lenalidomide be made available through the NHS. We are pleased that the Committee recognises the urgent requirement for new agents to meet the unmet need of patients with this universally fatal disease and that the Government and NICE have acted in a timely manner to implement the recently introduced "end of life" proposals in introducing this drug. Lenalidomide clearly meets	Comments noted. See FAD sections 4.7 and 4.17 to 4.19 in particular. Also, please note that the Appraisal Committee considered that rigorous data collection is needed on the life-extending benefits of lenalidomide when used in people who have had two or more prior therapies (see FAD section 6.1).

Consultee	Comment	Response
	all the criteria for these new proposals. It has been the experience of those using this and other novel agents introduced over the last 12-18 months that the management of toxicity and side-effects improves significantly as familiarity with the drug increases. The highest percentage of side-effects appear to occur early in the treatment course and most are low grade and easily managed with simple dietary and medical intervention.	
	We do believe the recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. The financial arrangements are robust and, in our opinion, should be relatively straightforward to implement. We are pleased to note that the Committee has considered feedback from stakeholders. We would take this opportunity to underline the importance that Health professionals attach to Guidelines and Multi-Disciplinary meetings, which serve to ensure all patients have access to the most effective treatment and that NHS resources are used cost effectively. We further seek to reassure the Committee that through our professional groups via guidelines, teaching and training, we will make every effort to ensure that the guidance is implemented responsibly and delivers maximum benefit to patients and the NHS.	Comments noted
	We are not aware of any equality related issues that need special consideration not covered in the ACD	Comment noted

Consultee	Comment	Response
RCPath	Yes. The College is very pleased indeed that the Committee , having considered the evidence of the ERG, and taking into account the price capping scheme offered by the manufacturer, and agreeing that Lenalidomide for myeloma fulfils the criteria of a life extending medicine, has recommended that Lenalidomide and dexamethasone be made available for patients with Myeloma at second relapse and beyond. As set out in our previous submissions we believe Lenalidomide to be a well tolerated , effective drug in patients with relapsed MM and we are in no doubt as to the importance of the Committee's decision and the positive impact it will have on the lives of people suffering with this disease.	Comments noted
	We believe the Committee, after rigorous examination of the all evidence has made the correct decision in recommending this technology be made available. We recognise and appreciate that the Committee has listened and agreed to feedback from our professional groups on a number of specific issues. However we note that it still expressed some doubts about the costs and disutilities for the adverse effects and anti-thrombosis prophylaxis for Lenalidomide. We wish to further reassure the committee that these doubts are unjustified as increasing clinical experience has demonstrated that side effects, such as they are, are mostly experienced early in the treatment course and lessen over time. They are very easily and cheaply managed and have proved in reality not to be the issue and challenge as they may have first appeared from the data	Comments noted (see FAD sections 4.7 and 4.17 to 4.19)

Consultee	Comment	Response
	which emerged from the trials. We are delighted that the desperate need of patients facing certain death has been acknowledged by Government and that NICE and the Committee have acted swiftly in implementing the new advice concerning end of life medicines and agreed that Lenalidomide for Multiple myeloma at second relapse meets all the criteria for the new advice to be applied.	
	We do believe the recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. In particular we feel that the capping scheme is simple and be easily to implement so the Health Service will not be faced with any hidden costs in ensuring that the manufacturer does bear the costs of Lenalidomide after 2 years. We understand it is necessary to ensure that NHS resources are used cost effectively and we wish to reassure the Committee that through our professional groups via guidelines, teaching and training, we will make every effort to ensure that the guidance is implemented responsibly so that this resource is used to deliver maximum benefit to patients.	Comments noted. See FAD section 4.16. Also, please note that the Appraisal Committee considered that rigorous data collection is needed on the life-extending benefits of lenalidomide when used in people who have had two or more prior therapies (see FAD section 6.1).
	We are not aware of any equality related issues that need special consideration not covered in the ACD	Comment noted

Comments received from commentators

Commentator	Comment	Response
Janssen-Cilag	We consider that the relevant published evidence to date has been taken into account. We consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	Comments noted
	Janssen-Cilag fully supports the need for patients with multiple myeloma to have access to the latest and most effective treatment options. Given the devastating nature of this condition, we agree that it was appropriate to consider the evidence based for lenalidomide in the context of the recent end of life arrangements. In reviewing the provisional recommendations of the Appraisal Committee, we believe that some of the details regarding the patient access scheme require further clarification. Firstly, we believe that the current threshold at which free of charge medicines would be provided is unclear as written. As a result we would like to request clarification of the treatment duration during which the NHS will cover the cost. As currently written, the guidance is open to interpretation on the following points: - Is it the two years of treatment that is most important, or the total number of cycles? For example, is the free of charge supply intended to become available after 2 years of continuous treatment (defined as 26 cycles of 28 days), or would free of charge supply be provided later than 2 years after starting treatment in the event that patients had breaks in their treatment. This would have the effect of spreading the 26 cycles over a period longer than 2 years and allowing retreatment with lenalidomide. - The assessment of clinical benefit and provisional recommendation has been based on MM009 and MM010 RCTs in which lenalidomide was continued until the occurrence of disease progression or unacceptable toxic effects. To prevent any confusion with the funding arrangements where two years of treatment is discussed we would like to suggest specifying that treatment is to be continued until disease progression.	Comments noted The cost effectiveness was calculated on the basis of treatment of 26 cycles normally given over 2 years, including treatment interruptions and reductions within cycles, and this was the basis on which the Committee made recommendations. The Patient Access Scheme takes effect from the 27th cycle. This has been clarified (see FAD 4.16 for further details). In the clinical trial lenalidomide was continued until disease progression or the occurrence of adverse effects – for further details please refer to the Summary of Product Characteristics.

Commentator	Comment	Response
	Secondly, we note that free of charge medication is only provided after two years/26 cycles of treatment (+£100,000 of costs to the NHS) and yet the median duration of treatment is less than one year. We wonder whether the extent to which the NHS will benefit from these arrangements has been fully assessed.	Estimates provided by the manufacturer state that for the group of patients who had received two or more prior therapies, the PAS applied to 17% of the people who had received two or more prior therapies, and that the average drug costs per patient in this group decreased from £59,800 to £51,800 with the PAS (see FAD section 3.21).
	We are not aware of any specific equity related issues.	Comment noted
	• The ACD for this guidance is entitled as follows 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy'. Given that the recommendation now only applies to second relapse and beyond, we believe that this title has the potential to be confusing as it refers to the population who has received "at least one prior therapy". We would suggest amending the title to reflect the population for which lenalidomide is recommended in this 2nd ACD: 'Lenalidomide for the treatment of multiple myeloma in people who have received two or more prior therapies'.	The appraisal remit included people with multiple myeloma who had at least one prior therapy and is applicable to this group. The positive recommendation is for people who have received at least 2 prior therapies. Section 1.2 of the recommendations refers to people who have received one prior therapy.
	• The ACD states page 5 under section 3.1: 'For people in whom bortezomib was contraindicated, for people who had received two or more prior therapies and for people who had received prior thalidomide (only one or two or more prior therapies) the comparator was dexamethasone' It is assumed that the contraindications NICE is referring to in the paragraph above are the ones indicated in the SPC of Velcade® and which are copied below for convenience: - Hypersensitivity to bortezomib, boron or to any of the excipients. - Severe hepatic impairment. - Acute diffuse infiltrative pulmonary and pericardial disease	The section referred to here is a description of the manufacturer's submission. The FAD does not give a detailed description of the contraindications of bortezomib, which is not the drug being appraised.

Commentator	Comment	Response
	Velcade® is not contraindicated in patients with peripheral neuropathy. The SPC states: 'Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment.' Also in the SPC*, recommendation is made to 'carefully monitor for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified'.	
	• The ACD states page 15 under section 4.4: 'Current NICE guidance restricts the use of bortezomib to first relapse because the use of bortezomib at subsequent relapses was found not to be cost-effective (NICE technology appraisal guidance 129), with ICERs of £77,000 or more per QALY gained.' We would like to point out that at the time of the appraisal of bortezomib for relapse myeloma (1st relapse and relapse/refractory) the supplemental advice from NICE for the appraisal of life extending medicines was not available yet. Therefore we would like to propose the inclusion of the following sentence to reflect the fact that the appraisal of bortezomib for relapse myeloma was undertaken under different circumstances than the one of lenalidomide. The added section is underlined below. 'Current NICE guidance restricts the use of bortezomib to first relapse because the use of bortezomib at subsequent relapses was found not to be cost-effective (NICE technology appraisal guidance 129 – <u>October 2007</u>), with ICERs of £77,000 or more per QALY gained <u>without the application of the Velcade Response Scheme</u>. <u>This appraisal of bortezomib was undertaken prior to the publication of NICE's supplemental advice for the appraisal of life-extending medicines</u>.	The FAD has been amended to take in to account that the figure of £77,000 referred to life years gained and not QALYs. However it is accurate as it stands as bortezomib was not found to be cost effective at second and subsequent relapse in Technology Appraisal 129. As the current appraisal is of lenalidomide, the details regarding bortezomib have only been included in the FAD to the extent necessary to explain the recommendations about lenalidomide. This guidance will be considered for review together with technology appraisal 129 (see FAD 7.2).
	• The ACD states page 16 under section 4.7:	

Commentator	Comment	Response
	'It noted that from patients' viewpoint lenalidomide is associated with a more favourable adverse effect profile than most other regimens and agents used in the management of relapsed multiple myeloma.' Given that lenalidomide has only been available for a relatively short period of time, Janssen-Cilag Ltd believes that the safety profile of lenalidomide has yet to be fully determined. As the statement is unsubstantiated and may be prejudicial against other regimens and agents given the lack of any robust comparison, head to head RCTs or observational studies, we would like to request that this is removed.	This view expressed here was that of patient advocates who attended a Committee meeting. Patient evidence refers to any information originating from patients and/or carers that may inform the appraisal of the technology. For the purpose of informing its technology appraisals, the Institute is looking for a concise and balanced overview that reflects the range of patient and carer perspectives including majority views and potentially important views that may be held by only a few patients. (see the Guide to the Methods of Technology Appraisal section 4.3)
	• The ACD states page 16-17 under section 4.7: 'It heard from clinical specialists and patient experts that lenalidomide might be particularly useful for people with pre-existing peripheral neuropathy in whom the use of bortezomib at first relapse is restricted.' - We would like to point out that an ongoing prospective study by Dimopoulos et al. has showed that 27% of patients with grade ≥ 2 pre-existing peripheral neuropathy receiving Revlimid and Dexamethasone (RD) experienced a deterioration of neuropathy. Also the SPC of lenalidomide indicates that Peripheral neuropathy is a common adverse drug reaction observed in patients treated with lenalidomide/dexamethasone: - As the above statement does not reflect the SPC* of Velcade® we would suggest specifying after the statement made by clinical specialists and patient experts that the SPC does not include any restriction for patients with pre-existing neuropathy. The SPC states: 'Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment'. Also in the SPC, a recommendation is made to carefully monitor for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified	This was the opinion of clinical specialists and patient experts who attended a Committee meeting. Clinical specialists and patient experts provide written evidence and attend Commitee meetings to help in the discussion of the technology being appraised. For the purpose of informing its technology appraisals, the Institute is looking for a concise and balanced overview that reflects the range of patient and carer perspectives including majority views and potentially important views that may be held by only a few patients. (see the Guide to the Methods of Technology Appraisal section 4.3)

Commentator	Comment	Response

Comments received from members of the public

Role*	Section	Comment	Response
Medical Practitioner	Section 1 Section 2 Section 3 Section 4 Section 5 Section 6	NICE should perform its primary duty in advising best practice based on best evidence in an independent, transparent & EXPEDIENT manner. The pharmaceutical industry needs NHS cost moderation but NICE should not weaken its independence by being Government`s cost control tool. Transparency would be preserved by declaring separate consultations on cost issues after clinical excellence recommendation reports. Cost analysis could also include prolongation of patient`s income tax payments & spending activity , both of which have positive fiscal effects re the cost of increased longevity , if cost is so important. Pharmaceutical companies should develop a symbiotic relationship with the NHS as each needs such a partnership. EVIDENCE BASED CARE SHOULD NOT BE COMPROMISED IN THIS PROCESS. The evidence strongly supports this recommendation and it should be implemented without further delay. Delay in availability of strongly evidence based interventions erodes the position of an allegedly independent arbiter of clinical excellence to one of a cost control arm of central government. I have enjoyed 13 months treatment free remission after 3 cycles of Bortezomib. Prior to this I enjoyed 54 months treatment free after high dose melphalan/autologous stem cell transplant. Vast series of one but I contend that paying tax , spending my disposable income and being a constructive member of society for	Comments noted. The purpose of NICE technology appraisals is to appraise not only the clinical effectiveness, but also the cost effectiveness of technologies. Technologies can be considered cost effective if their health benefits are greater than the opportunity costs measured in terms of the health benefits associated with programmes that may be displaced to fund the new technology. In other words, the general consequences for the wider group of patients in the NHS are considered alongside the effects for those patients who may directly benefit from the technology of interest. With regard to your comment on patient's income tax and spending activity, the Institute works in a specific context; in particular, it does not set the budget for the NHS. The appropriate objective of the Institute's technology appraisal programme is to offer guidance that represents and efficient use of available NHS and Personal Social Services resources. For these reasons, the reference-case perspective on costs is that of the NHS and PSS. For further details, please see the Guide to the Methods of Technology Appraisal

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', '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
		this time Â has been a worthwhile outcome for the NHS investment in the management of my condition.	http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
NHS Professional	Section 4	In clinical practice, Thalidomide is widely used. There is now a licensed preparation. At the moment, clinicians are requesting funding on exceptional grounds as thalidomide causes peripheral neuropathy. Where in this guidance will PCTs be able to clarify when Thalidomide should be used first as it is more cost effective for the NHS if the generic (unlicensed) preparation continues to be used. This guidance appears to discount Thalidomide as its unlicensed (which it isn't any more). Is there any evidence of effectiveness and harms vs Thalidomide?	Thalidomide is licensed for use in multiple myeloma as a first line treatment and does not hold a licence for relapsed disease. The Committee noted a lack of evidence on which to consider a comparison between lenalidomide and thalidomide. In addition the extent to which thalidomide is used for relapsed multiple myeloma in clinical practice is unknown. These issues are particularly apparent in the subgroups who have received two or more prior therapies (see FAD 4.4).
Patient	Section 1 Section 2 Section 3	Brilliant news but why is it only recommended after two therapies, is this because this is when the drug is most effective or is this to cut costs a little. The drug seems to have a lot of side affects, are the side affects manageable/treatable in most cases? Why on earth does it cost this amount of money to produce these drugs, are they technically difficult to manufacture or does the ingredients/chemicals cause the cost to be so high? This is far too technical for me to understand but what I did understand was the possibility of extending life for myeloma patients for approx 3 years. This has to be good news because in those three years more treatments will evolve and further life extensions may be possible. I am pleased at the way the committee has fully analyzed the data and weighed up the evidence. I am even more pleased that the decision to make the drug available on the NHS has been reached. Thank you also to Celgene for funding treatment beyond two years.	The Committee concluded that the len/dex combination improved health outcomes in people with relapsed multiple myeloma when compared with dexamethasone. This included people who had received either one or two or more prior therapies. Lenalidomide is recommended after 2 or more prior therapies because it was considered to be cost effective when so used under the conditions of a patient access scheme. The Department of Health in England and the Department of Health and Social Services in Wales accepted the consideration of this scheme by NICE.For the treatment of multiple myeloma in people who had received only one prior therapy, the Committee concluded that lenalidomide would not be a cost-effective use of NHS resources. The purpose of NICE technology appraisals is to appraise not only the clinical effectiveness, but also the cost effectiveness of technologies.

Role*	Section	Comment	Response
			Technologies can be considered cost effective if their health benefits are greater than the opportunity costs measured in terms of the health benefits associated with programmes that may be displaced to fund the new technology. In other words, the general consequences for the wider group of patients in the NHS are considered alongside the effects for those patients who may directly benefit from the technology of interest. For further details, please see the Guide to the Methods of Technology Appraisal http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	Section 5	Please consider the effects of a 3 month wait for this treatment to become available. Please consider issuing the drug for patients who need it now.	Comments noted. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally ***within*** 3 months from the date that NICE publishes the guidance.
	Section 7	The review date for technological guidance seems fair, although a partial review in January 2009 may prove useful.	The guidance on this technology will be considered for review in October 2010 together with the guidance on bortezomib (NICE technology appraisal guidance 129).
Patient	Section 1	Initially restrict use of Bortezomib and Lenalidomide to treatments of last resort as judged by doctors, i.e. no other suitable treatment. Insist on recording treatment in full, following trial procedures. Use the experts (e.g. Royal Marsden) to determine data needs, and collate all UK data for immediate use by doctors, and by NICE at review stage. Allow selected specialist doctors more flexibility in choice of patients, to improve knowledge at all stages of the disease. Consider patients like me taking a new trial, then Lenalidomide on	Comments noted. The Institute undertakes appraisals at the request of the Department of Health. The remit for this appraisal is to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications for the treatment of multiple myeloma in people who have received at least one prior therapy. The recommendations of the Appraisal were developed in line with published process and

Role*	Section	Comment	Response
	Section 2	relapse to regain fitness (Lenalidomide gives me almost instant full remission), before repeating the process, hence turning Myeloma into a manageable disease. Too few patients have been treated to be sure about side effects and long term effects. Post code lottery has denied many doctors access to these drugs. There is a learning curve, and this should be acknowledged in costings. The patient is not the only one to gain from spending £4368 per cycle. Try to discourage doctors from using Lenalidomide to simply stabilise disease, i.e. encourage them to look for suitable new drugs and trials to give remission rather than stability.	methods. It is important that the methods used to inform the Appraisal Committee's decision-making are consistent. For this reason, the Institute has adopted the approach of using a 'reference' case for cost-effectiveness analysis; this was chosen as most appropriate for the Appraisal Committee's purpose. For the considerations of the Appraisal Committee explaining the recommendations for this appraisal please see section 4 of the FAD.
	Section 3	You do Myeloma patients a dis-service by forcing manufacturers into your preset format, comparing one drug with another, and deciding which is best. For Myeloma patients older treatments generally can only be used once. When the patient is lucky they may give good remission with minimal side effects. Any additional new drug or treatment is of potential benefit, even if only giving 3 months remission. Do not lump all results together in an average! The cost should be broken down into "Full remission" (worth the expenditure) Fails to prevent progression (don't waste money once position is clear) Partial remission (normally stop when results show treatment has been ineffective, but maybe allow some stabilising treatment). You quote figures like £43,000 and more. I got full remission on 3 cycles (<£13,500).	
	Section 4	Put a Haematologist on your committee. Don't worry about the sequence -that's for the specialists to consider on a patient by patient basis. Concentrate on adding new drugs/treatments to the armoury. Let them become routine only when fully studied (e.g. 3-4 years).	For the professional/specialist and patient/carer groups, as well as individuals selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators involved in this appraisal,

Role*	Section	Comment	Response
	Section 5 Section 6 Section 7	It is said there is a new treatment arriving every year. Excellent - each one becomes the one of last resort, and subject to NHS testing by all the specialist doctors. One day the specialists will decide to drop the older chemo treatments. It is next to useless worrying about whether Bortezomib is better than Lenalidomide. It all depends on how it works for each individual patient. Don't trust the statistics, there are too few patients, and too much variability. Each patient is almost unique. We just want the chance to achieve that next remission! I have done 16 years with every drug going, and I want another 20 years to put me in my working 90s! Minimise costs by using each new drug as drug of last resort. If no patient is left stranded, or told to "go away and die" as a commissioner told me, then there will be no screaming patients and families in the media. That's where I am today. I want a boost with Lenalidomide. My appeal to the public is due in the Oxford Mail tomorrow. I shall probably remain in this position until 3 months after you publish your final decision. I am "all right Jack". I am fit enough to join some manufacturers trial. Others are not, and it's my job to help them, so please help me to help them. Bortezomib should be treated just like Lenalidomide. To patients they both have the same result, provided they work. We need both, each being a fallback drug in case the other does not work. Please make it possible for NHS doctors to collect and collate the information for you to make valid decisions. These decisions should be independent of manufacturers trials, which are designed for showing drugs are safe at the limits, and to help with their marketing.	please see Appendix A of the FAD.