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 Appraisal Consultation Document (ACD) issued October 2008

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	Referring to paragraph 4.2 of the ACD and highlighting the appraisal committee's note of the importance that patients, their carers and physicians place on having effective options to treat multiple myeloma, we have focused our responses to the ACD on patients who have received at least two prior therapies as there are more limited treatment options available to patients and physicians at this stage of the disease. Thus, we are not responding to comments regarding lenalidomide treatment in patients with only one prior therapy. Thus we are not responding to the suggestion that bortezomib is frequently used in combination with dexamethasone and this combination should be examined (page 15 in the evaluation Report and page 13 (4.3) of the ACD). We are not including a comparison with this combination because it is not a licensed use of either drug, there is insufficient evidence on its efficacy, and it is not recommended by NICE. Thank you for the opportunity to respond to the ACD. Herewith are our remarks.	Comments noted. No action required.
Celgene	**i) Do you consider that all of the relevant evidence has been taken into account?** We believe that the appraisal considered all of the relevant evidence for the use of lenalidomide in previously treated multiple myeloma that was available at the time of the appraisal. We pointed out in our original submission that the MM-009/010 trials are ongoing and continue to mature. Most importantly, we highlighted in our original submission that the median overall survival (OS) with lenalidomide/dexamethasone (Len/dex) had not yet been reached, as <50% of patients in the Len/dex arm had died at the time of the most recent data analysis and that as the data mature it is possible that the median OS with Len/dex will increase further.	Comments noted. No action required. See FAD sections 4.9 to 4.11 and 4.15.

Consultee	Comment	Response
	We will be adding a number of additional references in support of our comments below, but these do not constitute new evidence.	
Celgene	**ii) 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 with the summarisation of the clinical evidence and are pleased that the committee recognises the clinical value of lenalidomide in managing patients with previously treated multiple myeloma. We thank the committee for commenting that the general structure of the submitted model was reasonable. However, we do not agree with the committee's determination that the use of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy is not cost effective use of NHS resources and we present our views below. As noted above, we will focus on multiple myeloma patients who have received two prior therapies and encourage the committee to recommend lenalidomide for patients who have received at least two prior therapies because there are few effective treatment options at this stage of the disease and lenalidomide offers a significant and cost-effective extension in patients survival beyond that offered by the current treatment options. **iii) 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?** As indicated in response to item 2 above, we do not agree with the Committee's findings on the economic value of lenalidomide. The Evidence Review Groups (ERG) Evaluation Report recommended changes in the cost effectiveness (CE) model. The ERGs key recommendations and comments include (from section 4.9 of the ACD) those listed below. We respond to each of the issues as presented	Comments noted. No action required.

Consultee	Comment	Response
	in the ACD. 1. Recalibration of the Len/dex survival to more closely reflect the publication (we accept this suggested change) – thus, decreasing Len/dex survival. The new analysis below uses the ERGs recommended recalibration in the Len/dex group. 2. Recalibration of the Dex survival using the mean MRC data (4.9 and 3.16). We do not agree with this approach (see details in the attached supporting response to ERG) because the resulting curve is less representative of the published curves (Dimopoulos et al. 2007; Weber et al. 2007) than our calculation. Figure 6 in the ERG report illustrates the problem of calibrating to the mean. It departs more from the target curve in the publication than the analyses we submitted using the median. Thus we have not accepted this recalibration in our reanalyses. We believe that using the mean places more emphasis on the tail of distribution where there are fewer patients and greater uncertainty. We point out in our response to the ERG report that the calibration is to help adjust for the cross-over effect and we believe that using the mean delays that correction and in doing so results in a less robust correction. 3. The submitted model results in higher overall survival with lenalidomide compared to the publications (Dimopoulos et al. 2007 and Weber et al. 2007). We investigated our model and can report the following details possibly contributing to the differences: a. Exclusion of non-evaluable patients from the model – we do not have sufficient data on these patients for response or TTP. The publications reported only overall survival (not post progression survival) and the non evaluable patients were included. Overall survival is the only efficacy data we have for these patients. Thus, it is problematic to include them in the model. The trial publications do not include these patients in the TTP calculations.	Comment noted. The Committee accepted that the approach to modelling overall survival in the dexamethasone arm was a matter of scientific judgement. The Committee concluded that ICERs estimated using the mean were more appropriate (FAD 4.9 to 4.11 and 4.15). Comments noted.

Consultee	Comment	Response
	b. Pooling all patients to ensure similar populations for each treatment. To ensure that identical patients were simulated on each treatment, the model selects individual patients from a population composed of all the evaluable patients from both trials, regardless of treatment to which they were randomised. Each patient is then modelled under each treatment option. This variance reduction technique not only reduces the sample size required to achieve stable results, it also removes any residual confounding present in the trial data. Randomization in clinical trials reduces differences across the groups and makes it possible to carry out unbiased comparisons of the average results. The inevitable differences between the groups, however, can become a problem when individuals are simulated over longer periods of time and the full extent of their course is used in computing the consequences of treatment. The pooling removes this problem but means that predictions will differ somewhat from the raw observed trial data. c. Data cuts differ from the published trials. The model includes data available at the time of its design (2005). The trials have continued to report findings and the publications used data from 2006. Since then more data have been reported. More patients have died, but the median overall survival has still not been reached for the Len/dex arm. The published plotted KM curves represent censoring and underestimate survival, particularly in the later portions of the curve.	
	4. The ERG CE results for the subgroups with two prior therapies were greater than £40,000/QALY (section 4.11). A reanalysis of these subgroups (new base case) is presented below incorporating the ERG recommended change in Len/dex survival, but not the use of mean instead of median (see details in our ERG response document and point 2 above). The cross-over impact observed in the clinical trials on the Dex survival was addressed by adjusting the post-progression survival of this group based on the median overall survival derived from the MRC data, rather than using	Comments noted. See FAD sections 4.9 to 4.11 and 4.15.

Consultee	Comment	Response
	the mean. (See point 2 above.) 5. Other identified issues (4.12) with the model base case are examined in sensitivity analyses presented below. a. Adverse event (AE) costs not fully included. The submitted model included costs of grade 3 and 4 adverse events according to location of care (hospital/physician surgery etc) and long term management. Included were anaemia, thrombocytopenia, neutropenia, hypercalcaemia, pneumonia, neuropathy, and deep vein thrombosis (DVT). Prophylaxis for DVT (comment from 3.17) was not included, but is included in a sensitivity analysis shown below. G-CSF (comment from 3.17) use was included in our resubmission in August (we agree with the reviewers that it was not included in our original submission) based upon the July comments from the reviewers. Details are shown in our response to the ERG report. b. Disutility for AEs not included (4.12 and 3.13). We did not find published values for the AEs in relevant oncology patients for the original submission. We have included disutilities for long term AEs obtained from patients with other disease (such as diabetes and breast cancer) in a sensitivity analyses shown below. A table in our response to ERG report shows the decrements applied and the sources of the values. c. Pre-progression utility value (0.81) for multiple myeloma patients used in our submission was considered too high, given the age of the trial population (4.12 and 3.12). This comment is surprising for two reasons. First, it is the value suggested by the ERG in the NICE appraisal of bortezomib (6.3.4.3 page 36; Green et al. Bortezomib in treatment of multiple myeloma) and appears to be the most relevant value available in the published literature, although the current reviewers sited 3 additional references (page 94 in Evaluation Report) which we have discussed in our response to ERG report attached as an appendix. Also the 0.81 value indicates these patients would accept a 19% chance of death to change from the asymptomatic pre-progression	Comments noted. See FAD section 4.15. The utility values used in the bortezomib were selected and implemented by the manufacturer of bortezomib in its additional analyses in response to questions raised in the evidence-review phase. The Appraisal Committee was concerned that the utilities assumed for patients with relapsed multiple myeloma may not accurately reflect the significant impairments in quality of life that these patients can experience. See the Technology Appraisal Guidance number 129, sections 3.5 and 4.6 at http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf. In this appraisal of lenalidomide, the Committee's considerations of utility values used in the model relate to appraising whether they reflect evidence and are applicable to the population for which its recommendations apply. It was considered that people with relapsed multiple myeloma on treatment may not have the same quality of life as the general population of a comparable age, and that the

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	state to normal health – a hefty penalty. Second, the ERG report and the ACD comment implies that a lower utility is more appropriate for patients in the preprogression state. This is tantamount to saying that keeping them alive for each additional year is less worthwhile than keeping a younger patient population alive. We do not believe that the appraisal committee wished to imply this age specific inequality message in the ACD. Despite our concerns about this utility value, we included sensitivity analyses around the utility values (+ 10%) in our original submission and provide these again with the new base case analysis. We did not adopt the values in the publications suggested by the reviewers (section 5.3.3.6 in the Evaluation Report).	average age of the population in the evidence did not match the average age of the population in whom lenalidomide is being appraised (FAD 4.12), and was aware that utilities values of the general population tend to decrease with age.
	d. The costs for routine management of myeloma and administration of the therapies used in our submission were questioned (4.12 and 3.17) and the comment made that they were not inflated to 2008. We agree that the costs should be inflated and we have done so in the reanalyses included below. To clarify the resources included, our model had one outpatient physician visit every other month before progression and one outpatient physician visit every month after progression, plus regular lab tests at frequencies based on whether the patient had progressed (page 131, Table 45 of our original submission). However, we agree that inadvertently the model left out the costs for outpatient visits. These are now included in the new analyses below. Examining the costs used in the bortezomib appraisal by NICE and the source document (Bruce et al. 1999) indicates that the value includes costs that are considered separately in our model. Thus the costs are not comparable. In addition, we are no longer comparing lenalidomide to bortezomib (thus the cost of this drug and its administration is no longer relevant) since we are focusing on patients who have already received at least two prior therapies for multiple myeloma.	Comment noted

Consultee	Comment	Response
	6. Cost effectiveness reanalyses for Len/dex therapy in the patient populations with 2 or more prior therapies for multiple myeloma, including those with prior thalidomide, compared to dexamethasone monotherapy findings are reported below. The results use the model adapted to reflect the ERG recommended recalibrated survival for Len/dex (point 1 above), inclusion of the outpatient visits, costs inflated to 2008 and the recommended sensitivity analyses all of which have been discussed above (Tables 2 to 7 and Figures 1 to 4 below). We have provided a fully executable copy of our adapted model with this response.	Comments noted.
	7. Furthermore, we would like to draw the appraisal committee's attention to the unique nature of lenalidomide as a treatment for multiple myeloma in that it is an oral therapy and is associated with a more favourable adverse effect profile (as noted in the ACD 4.6). It is the combination of these factors that enables patients to remain on long-term treatment and continue to benefit from lenalidomide until their disease progresses. It is the ability for patients to remain on treatment and continue to receive long-term benefits that is the key cost driver in the cost-effectiveness of lenalidomide because costs continue to accrue as patients continue to benefit from treatment. Following the publication of the ACD there has been significant media coverage, which has included a coalition of patients groups (including Myeloma UK, MacMillan Cancer Support and Leukaemia CARE) calling on the Department of Health, NICE and Celgene to work in partnership to overturn the preliminary negative recommendation for those seriously ill patients who could benefit from lenalidomide through improvements in their life-expectancy and quality of life. In response to the call from the coalition of patient groups we have proposed a price capping scheme to the Department of Health that will enable patients who have received at least two prior therapies to continue to enjoy the benefits of long-term treatment with lenalidomide. Specifically, we have proposed a scheme that will cap the maximum cost to the NHS for an	Comments noted. In the FAD lenalidomide is recommended for people with multiple myeloma who have at least 2 prior therapies under the conditions of the patient access scheme whereby the manufacturer pays for cycles beyond 26 cycles (normally 2 years), continued until disease progression.

Consultee	Comment	Response
	individual patient at two years of treatment (26 cycles each of 28 days). The cost of lenalidomide for those patients who remain on treatment beyond two years will be met by Celgene. We propose to implement the scheme through the existing Pregnancy Prevention Programme and in doing so believe that the scheme would have neutral burden or arguably reduce NHS burden. The scheme improves the cost effectiveness of lenalidomide and importantly removes the uncertainty over the long-term costs to the NHS. The scheme reduces the ICERs using the new updated base case as discussed above to £30,350/QALY for patients with 2 prior therapies and £28,941/QALY for patients with 2 prior therapies, including thalidomide. These ICERs are within the range of those for other medicines for serious life-limiting diseases which have received positive NICE recommendations. We include, as an appendix, a copy of a letter that we have sent to the Department of Health outlining our proposed scheme and have been asked by the Department of Health to inform you that we are in discussions with them regarding this scheme.	
Celgene	RESULTS: Details of results provided by the manufacturer are not reproduced in this table. For full text, please see the manufacturer's comments on the ACD issued October 2008.	Comments noted
Celgene	**iv) Are there any equality related issues that need special consideration that are not covered in the ACD?** The equity issue we have raised above in 5c. The ACD comments that the quality of life for the older pre-progression patients should be lower implying it is less worthwhile than keeping a younger patient population alive. We suggest that this be modified to avoid the inequality message. As further indication of the value to use in this population, the ERG comments (Bortezomib in treatment of multiple myeloma, Green et al, 2006) indicate that 'a health state value between 0.644 and 0.789 may be appropriate for patient groups with MM. However, Kind et al (1998) have reported health state values in the UK general population by age group, valued	The Committee's considerations of the age of people on which the assumed utility values used in the model were based relate to appraising whether they reflect evidence and are applicable to the population for which its recommendations apply. It was considered that people with relapsed multiple myeloma on treatment may not have the same quality of life as the general population of a comparable age, and that the average age of the population in the evidence did not match the average age of the population in whom lenalidomide is being appraised (FAD 4.12), and was aware that utilities values of the general population tend to decrease with age. Gain in QALYs conferred by lenalidomide over its comparators will result from the model by way of more time assumed to be spent in states with higher utility values

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	using the EQ-5D, with those aged between 60-69 years ranging between 0.829-0.806.' Thus, a health state value near 0.80 is likely appropriate for the population in pre-progression.	(e.g.complete response and progression-free) and less in those with lower utility values (post progression). The utility values implemented in the model were selected by the manufacturer with the rationale that they were based on the most suitable evidence available. As the utility values of people with relapsed myeloma at older have not been identified it is unknown what affect this would have on the ICER.
Myeloma UK, Leukaemia CARE, Leukaemia Research and the Rarer Cancers Forum	**i) Do you consider that all of the relevant evidence has been taken into account?** 1.1 Lenalidomide is the subject of two high-quality randomised controlled trials out of which has come a substantial body of impressive data. The body of data appears to have been considered in full and whilst we are pleased that lenalidomide has been recognised as a clinically effective treatment, we are frustrated that the Institute and the manufacturer remain unable to remove the uncertainty around the effectiveness of a treatment that is the subject of crossover in trials. The ERG report states "the main threat to validity for clinical effectiveness data is the high level of crossover in the trials…This is a problem in many assessments of new chemotherapy in end stage cancer and it would be unethical to undertake trials that did not allow for such crossover. However, this does introduce uncertainty into the results". Given the admitted frequency of crossover and its substantial consequence on the validity of trial data, we recommend the Institute establishes a standard method to more justly assess treatments which are penalised by the current appraisal process for being the focus of trials unblinded early because of their superior clinical effectiveness. That the Appraisal Committee and the manufacturer cannot reduce the uncertainty around the data for a treatment that has such an impressive body of evidence supporting it is surely incongruous with their necessary skill sets.	Comments noted.

Consultee	Comment	Response
Myeloma UK, Leukaemia CARE, Leukaemia Research and the Rarer Cancers Forum	1.2 We applaud the improved understanding of myeloma that is demonstrated by the Committee, recognising the heterogeneous nature of the disease and that choice of therapy for patients is influenced by several factors. The Committee also notes that the optimal sequence of treatments is "as yet unclear". Given the acknowledged nature of the disease and the impressive body of evidence for lenalidomide, we urge the Institute, the Department of Health and the manufacturer to discuss ways in which the NHS price can be reduced and / or an appropriate risk share scheme can be introduced to reduce uncertainty in a timeframe that is in the best interests of patients.	Comments noted. In the FAD lenalidomide is recommended for people with multiple myeloma who have at least 2 prior therapies under the conditions of the patient access scheme whereby the manufacturer pays for cycles beyond 26 cycles (normally 2 years), continued until disease progression.
	ii) 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? 2.1 We note that the ERG considered that the "approach taken to modelling is reasonable" and that the randomised controlled trials are "good quality". Further, the Committee recognises that a good job has been done within the manufacturer's model with regards attempting to account for the crossover in the trials, and acknowledges the appropriate use of the historical MRC data. The Committee "accepted that these data represented the best available survival data for people with multiple myeloma to be used in extrapolation of overall survival". Despite this, it is clear that there is also an inherent distrust of the manufacturer's submission, with the Committee considering that the ERG's approach "resulted in more plausible estimates of cost effectiveness than those presented by the manufacturer". What justification can the Institute supply that the ERG modelling is more valid? It is evident from the ERG report that the manufacturer corrected errors throughout the	Comments noted. In their considerations of cost effectiveness the Committee consider the strength of the supporting evidence, the robustness and appropriateness of the structure of the economic model, the plausibility of the inputs into and the assumptions made in the economic model. Once the Committee has agreed on the modelling approach and inputs that it considers to be most appropriate, ICERs incorporating those assumptions are identified as the most plausible. In this appraisal those ICERs were calculated by the ERG using the manufacturer's model.

Consultee	Comment	Response
	process; we assume therefore that the manufacturer is willing for the evidence to be the best it can be. It is unclear to us why or how we can be confident that the ERG is not making negative and pessimistic assumptions about the data to the detriment of patients. In the same way that the Institute may assume that the manufacturer overestimates the value of their product, those externally may assume that the ERG would underestimate the benefits. For is it not the case that the clash between the manufacturer and the ERG is all about different interpretations of what is scientifically most appropriate? Indeed, the ERG states that its own modelling has many "matters of judgement and preferred assumptions" throughout it. As informed stakeholders, we imagine that the likely QALY is in between the two estimates, which would surely bring the QALY of lenalidomide within an acceptable range for further discussion. Ultimately, we find it unacceptable for the Institute to turn a treatment down on the basis of uncertainty which is determined by an evidence review group who admit that its own considerations were tainted with uncertainties. 2.2 Regardless of whose modelling is interpreted as 'more accurate', we recognise that lenalidomide is an expensive treatment. However, even if the ERG modelling is considered the most plausible, the QALYs for patients who have had >1 prior therapy with and without prior exposure to thalidomide are still within touching distance of what NICE deems acceptable. In view of the undisputed clinical evidence a 'no' at FAD stage would represent a huge failure from all involved to effectively interpret an impressive set of data and show willing to strive for the best for all patients. There is now also a window of opportunity for NICE, the company and the Department of Health to find a solution together. Such an approach would complement the national agenda of promoting more flexible pricing and availability of	In the FAD lenalidomide is recommended for people with multiple myeloma who have at least 2 prior therapies under the conditions of the patient access scheme whereby the manufacturer pays for cycles beyond 26 cycles (normally 2 years), continued until disease progression.

Consultee	Comment	Response
	new drugs, as set out in Prof Mike Richard's report Improving access to medicines for NHS patients.	
Myeloma UK, Leukaemia CARE, Leukaemia Research and the Rarer Cancers Forum	**iii) 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?** 3.1 We do not. As the recommendation stands, patients who are suitable for lenalidomide will not routinely get access to it. It is now government policy that patients can pay for treatments out of their own pockets if the NHS does not provide them. It is clear that where a treatment costs only a few pounds a day, 'topping up' is unlikely to prove a serious financial burden. Lenalidomide, however, costs £4368 per month; this top-up cost will be affordable to very few people. A failure by NICE to reconsider its draft will make it increasingly difficult for patients to get access to this important advance in the treatment of myeloma. For this to remain a 'no' at FAD stage will effectively mean that the Institute are folding into their guidance the impossible choice between financial hardship and less efficacious treatment for relapsing myeloma patients.	Comments noted. In the FAD lenalidomide is recommended for people with multiple myeloma who have at least 2 prior therapies under the conditions of the patient access scheme whereby the manufacturer pays for cycles beyond 26 cycles (normally 2 years), continued until disease progression.
Myeloma UK, Leukaemia CARE, Leukaemia Research and the Rarer Cancers Forum	iv) Are there any equality related issues that need special consideration that are not covered in the ACD? 4.1 The ACD explains that the utility values used to generate the lenalidomide QALY were based on the utility of the general public at a median age of 54. In point 4.12 the Committee communicates its unease that someone of 54 is "considerably younger than the average population at age of people who usually developed multiple myeloma". Here the Institute is implying that because myeloma patients are generally older than 54, it is not prudent to correlate health gains that a 54 year old might enjoy to a myeloma patient because health gain is not worth as much in older people	The Committee's considerations of the age of people on which the assumed utility values used in the model were based relate to appraising whether they reflect evidence and are applicable to the population for which its recommendations apply. It was considered that people with relapsed multiple myeloma on treatment may not have the same quality of life as the general population of a comparable age, and that the average age of the population in the evidence did not match the average age of the population in whom lenalidomide is being appraised (FAD 4.12), and was aware that utilities values of the general population tend to decrease with age. Gain in QALYs conferred by lenalidomide over its comparators will result from the model by

Consultee	Comment	Response
	that in younger people. It is our view that with this statement the Institute is exercising age discrimination.	way of more time assumed to be spent in states with higher utility values (e.g.complete response and progression-free) and less in those with lower utility values (post progression). The utility values implemented in the model were selected by the manufacturer with the rationale that they were based on the most suitable evidence available. As the utility values of people with relapsed myeloma at older have not been identified it is unknown what affect this would have on the ICER.
	4.2 Further, Myeloma UK wishes to point out that in the bortezomib monotherapy appraisal the Institute directed Johnson & Johnson to use this same utility value when converting Life Years Gained into QALYs. That the ERG wants consistency between the appraisals with regards the administration and medical management costs for bortezomib but employs unexplained misgivings about the manufacturer using identical utility values to the bortezomib appraisal is spurious. It implies that the ERG wants the manufacturer to comply only with the component of the bortezomib appraisal that discredits the cost effectiveness of lenalidomide.	This is not correct. The utility values used in the bortezomib were selected and implemented by the manufacturer of bortezomib in its additional analyses in response to questions raised in the evidence-review phase. The Appraisal Committee was concerned that the utilities assumed for patients with relapsed multiple myeloma may not accurately reflect the significant impairments in quality of life that these patients can experience. See the Technology Appraisal Guidance number 129, sections 3.5 and 4.6 at http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf. The ERG stated that routine medical management costs for multiple myeloma are unknown. However, it noted the figure used in the bortezomib appraisal as a potential value.
BSH/UKMF NCRI/RCP/ RCR/ACP/ JCCO RCPath	**1) Do you consider that all of the relevant evidence has been taken into account?** Yes	Comment noted
BSH/UKMF NCRI/RCP/ RCR/ACP/ JCCO RCPath	**2) 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 are pleased that the committee have concluded that lenalidomide/dexamethasone combination therapy improves outcomes in people with relapsed multiple myeloma. We are concerned, however, that there appear to be several	

Consultee	Comment	Response
	misinterpretations of the evidence, leading to potentially unsound conclusions, all of which would serve to increase the cost per QALY unjustifiably. A) A fundamental misinterpretation of the clinical trial data by the ERG is presented on page 87 of the report by the Peninsula technology Assessment Group. This relates to "uncertainties" over the overall survival of patients treated with Dex. Here it is stated that, because the recent report from the Mayo group indicated that the improved survival of patients with multiple myeloma today is because of the advent of new therapies, therefore the overall survival of patients treated with Dex may be better than calculated from the MRC data. The group conclude, we believe without justification, that therefore it would be better to "populate the cost-effectiveness model with data for Dex taken from MM-009 and MM-010 with patients who crossed over to Len censored". B) This demonstrates a fundamental misunderstanding of the trial structure and rationale – and amounts to suggesting that the comparator arm consist of patients who start treatment with Dex, then switch to Len/Dex!! To re-iterate, the improvement in survival of patients in the last decade is due to the use of new therapies, including Bortezomib and lenalidomide, and hence for patients treated on Dex alone (the comparator arm), no such improvement in survival is expected, and therefore the MRC data are still appropriate to the economic evaluation. It must surely be obvious that using the same treatment for the same disease is not going to lead to a change in response over time given that the fundamental pathology of the disease and the efficacy of the drug remain the same. C) A second misconception is presented on page 31 of the same report. The authors state that the use of outcome measure to predict OS is "a recurring problem in MM	Comments noted. The Committee accepted the need for adjustment of cross-over effect and discussed lack of evidence for improvement in survival over time since the MRC trials (see FAD 4.9). Comments noted. The Committee took outcomes of response rates and progression-free survival into consideration (see FAD 4.2 and 4.5). In the economic evaluation, both progression-free and overall survival were

Consultee	Comment	Response
	research" and that complete response rate is not valid surrogate for OS, and neither is PFS. This is a problem with the ERG focussing on particular papers rather than reviewing all the relevant literature. Both the papers referenced are from the Little Rock group who have a unique and particularly aggressive treatment protocol for newly diagnosed patients, and the second paper was evaluating the impact of including Thalidomide. The first paper indeed confirms the importance of PFS for OS. Balanced against these papers is a wealth of data from thousands of myeloma patient cohorts that confirms that depth of response, i.e. CR rates, predicts for PFS and OS. Some examples are given below including the paper in the NEJM reporting on the UK MRC-sponsored Myeloma VII trial: 1. Child JA et al. ,NEJM, 2007, 348:1875 2. van de Velde et al, Haematologica, 2007, 92:1399 3. Lahuerta et al, J Clin Oncol, 2008, Epub 4. Niesvizby et al, Brit J Haematol, 2008, 143:46 The last relates to patients in the relapsed setting.	modelled (see FAD 3.8).
	D) The evaluation by the ERG of the ICER using Bortezomib as comparator for patients with only one prior therapy took the maximum number of cycles to be 11, whereas the median number of cycles received by patients in the APEX trial was 7. Eleven cycles was the maximum allowed for patients who achieved CR.	Comment noted. The Committee considered evidence comparing the clinical and cost effectiveness of lenalidomide with bortezomib for patients who have had one prior therapy – for details see FAD 4.6, 4.11 and 4.14. This guidance will be considered for review together with technology appraisal 129 (see FAD 7.2).
	E) 3.17. The ERG commented that the costs of routine medical management assumed in the model are too low. Whilst we have no specific expertise in health economic analysis technology, we wish to point out that, given the better toxicity profile of the technology (see Section 4.6), it would be hardly surprising that these costs would be lower than the figures accepted in the appraisal of bortezomib. In addition we would like to make clear that G-CSF is seldom used in the UK and Europe for the management of adverse effect of bone marrow suppression and in clinical practice	The ERG stated that routine medical management costs for multiple myeloma are unknown. However, it noted the figure used in the bortezomib appraisal as a potential value. The Committee accepted the manufacturer's approach to avoid double counting of costs included in routine management. The Committee also accepted that estimates of cost effectiveness were not sensitive to assumptions about the use of G-CSF and DVT prophylaxis. The major impact on cost effectiveness was the approach to modelling overall survival for dexamethasone (see FAD 4.15).

Consultee	Comment	Response
	most clinicians would reduce the dose of lenalidomide according to the SMPC. An important point to make is that the incidence of neutropenic infections in the MM-009 and MM-010 studies was very low (1.7%). This has been born out by subsequent clinical experience and is what informs clinicians' judgement that GCSF is not usually needed. Finally, anti-thrombotic prophylaxis can be effectively achieved with low dose aspirin in >90% of patients on Lenalidomide / dexamethasone, and the cost of warfarin or low molecular weight heparin in the remaining 5% is negligible (no additional outpatient attendances would be required for monitoring of INR over and above regular outpatient attendances).This policy will be incorporated in the new national Myeloma guideline being developed by the UKMF.	
	F) The committee comment that there is uncertainty in the results of the indirect comparison (4.5). Such uncertainty is inherent in the issues around treating relapsed and refractory myeloma, because of the nature of the necessary ethics of the studies which inform the process and also the pace at which the therapeutic options are evolving, e.g. the current practice of using Bortezomib with dexamethasone.	Comment noted
	G) We are pleased that the committee noted that lenalidomide has a more favourable adverse effect profile, and is particularly useful for patients with pre-existing neuropathy, in whom the use of bortezomib is restricted (4.6). We argue that the increased risk of venous thrombosis and embolism are effectively prevented by the use of low dose aspirin in the majority of patients, and for the small minority who require warfarin or low-molecular weight heparin, the additional costs would be negligible as such patients would routinely be under regular monitoring for their relapsed disease.	Comment noted

Consultee	Comment	Response
	H) We wish to point out that the costs and utility decrements (3.12) are based on a single study of a small number of patients receiving intensive chemotherapy followed by autologous stem cell transplantation, where a utility value of 0.81 is assigned to patients in remission, and a value of 0.64 assigned to those with progressive disease. We note that these values are based on the utility of the general public at a median age of 54 years, and are surprised that the ERG have applied them to the patient population under consideration. Given that the median age at diagnosis is 65 years, patients at first and subsequent relapse would be around 70 years of age, and we consider that the use of utility values based on a healthy population aged 54 years is inappropriate, and constitutes discrimination against an elderly population.	Comments noted. The Committee acknowledged that the median age of people with multiple myeloma was greater than the population in the trial. The Committee was also aware that people with relapsed multiple myeloma on treatment may not have the same quality of life as the general population of a comparable age. The values of 0.81 and 0.64 referred to in the comment were implemented in the model by the manufacturer with the rationale that they were based on the most suitable evidence available, and commented on by the ERG. Gain in QALYs conferred by lenalidomide over its comparators will result from the model by way of more time assumed to be spent in states with higher utility values and less in those with lower utility values. As the utility values of people with relapsed myeloma at the ages referred to in the comment have not been identified it is unknown what affect this would have on the ICER .
BSH/UKMF NCRI/RCP/ RCR/ACP/ JCCO RCPath	**3) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation for the guidance to the NHS?** Based on the points raised above, we do not feel that the provisional recommendations are sound, nor do they constitute a suitable basis for the preparation for the guidance to the NHS. We note that the effect of all the points on which we disagree with the ERG would have been to increase the cost per QALY as estimated by the ERG. We believe therefore that the ERG should re-model the cost calculation to take these points into consideration when the effect should be to lower the estimated cost per QALY to a figure which more closely approaches the figure of £30,000, usually considered affordable. We worry that having identified a number of fundamental misconceptions and misunderstandings in the interpretation of the clinical evidence that similar errors may have occurred in assembling of the economic evidence on which having no specific expertise we are not qualified to comment. We are also aware that NICE will shortly be bringing out	Comments noted. The Committee took in to consideration the Institute's supplementary advice to Appraisal Committees on end of life treatments when formulating the final recommendations (FAD 4.17 to 4.19)

Consultee	Comment	Response
	specific guidance to its appraisal committees with regard to life-extending medicines licensed for terminal illnesses affecting small groups of patients. This guidance may be relevant to the technology and, if so, we hope that the committee take this guidance into account before issuing the FAD.	
BSH/UKMF NCRI/RCP/ RCR/ACP/ JCCO RCPath	4) Are there any equality related issues that need special consideration that are not covered in the ACD? Please see the point made above with regard to the older age group of the patients for whom this technology is relevant, and the concern that the current utility values discriminate against this older population.	Comments noted.
Macmillan Cancer Support	**1. Do you consider that all of the relevant evidence has been taken into account?** 1.1 This is a very difficult patient group to treat – with limited options for many that relapse – time to progression and response rates including overall survival are better with lenalidomide plus dexamethasone compared to dexamethasone alone. This treatment therefore presents patients with a much better option than is currently routinely available within the NHS.	Comments noted. The Committee accepted that the clinical effectiveness of lenalidomide in combination with dexamethasone compared with dexamethasone alone has been shown (see FAD 4.5). The Appraisal Committee is required to make decisions on the basis of both clinical and cost effectiveness (see Guide to the methods of technology appraisals http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf, section 6.2).
	1.2 As outlined in point 4.2 of the ACD it is acknowledged that patients, carers and physicians all believe that lenalidomide is an important advance in treatment for multiple myeloma and that it is vital that there are treatment options available within the NHS for treating patients after relapse. We are concerned that this does not seem to have any weight in the evaluation of the evidence and would ask the Committee to reconsider the needs of this small patient population.	Comments noted. The Committee was aware that there were fewer treatment options available with subsequent relapses of the disease (FAD 4.18).
Macmillan	**2. Do you consider that the summaries of clinical and**	

Consultee	Comment	Response
Cancer Support	**cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** 2.1 We are concerned that the EQ5D measure of quality of life does not have a dimension which adequately captures energy or fatigue. One of the main symptoms of myeloma is excessive tiredness and lethargy due to a lack of red blood cells (anaemia). Therefore energy and fatigue are very important considerations in treatment of myeloma patients, particularly as their disease progresses and must be considered by the Appraisal Committee. This is not captured in the utility scoring and as this is a known shortcoming in the analysis we would like to see how this issue is being considered by the Appraisal Committee. 2.2 We are also concerned that when clinical trials allow patients to cross over to the other arm of the trial at unblinding, this degrades the clinical trial data, as described in point 3.4 of the ACD. This makes the data less compelling because end points are not reached in the control arm. We would ask the Appraisal Committee to consider this important clinical trial data again.	The utility values were based on a study that evaluated intensive chemotherapy followed by myeloablation and autologous stem-cell transplantation in people with multiple myeloma (see FAD 3.12 and 4.12). Comment noted. The Committee were aware of the issue of crossover and the adjustments in the economic model to compensate for this (see FAD 4.9, 4.10 and 4.15).
Macmillan Cancer Support	3. 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? 3.1 We do not believe that the provisional recommendation constitutes suitable guidance to be implemented by the NHS. 3.2 As outlined above (point 1.1) we are concerned that the evidence supplied by patients, carers and clinicians does not seem to have been given significant weight in the consideration of the evidence.	Comments noted.
Macmillan Cancer Support	4. Are there any equality related issues that need special consideration that are not covered in the ACD? 4.1 The NICE Citizen's Council recommends that NICE and its advisory bodies should take the severity of a disease	The Committee considered the severity of the condition in coming to its recommendations (see FAD 4.14).

Consultee	Comment	Response
	into account when making decisions. The NICE Board has subsequently accepted these recommendations and we would urge the Appraisal Committee to take these recommendations in to account now so that the most patients will be able to benefit. We would like to see, in the 'Evidence and interpretation' section, whether the Appraisal Committee was persuaded in this instance to take the severity of this condition into consideration alongside the cost and clinical effectiveness evidence.	
Macmillan Cancer Support	5. Other comments 5.1 We would urge manufacturers to put forward a risk-sharing agreement to reduce the QALY to make these treatments more likely to be considered cost effective. 5.2 According to the UK Statistics Authority the 'Cancer statistics registration – Registrations of cancer diagnosed in 2005, England' stated that there were 3,243 newly diagnosed cases of multiple myeloma in 2005. This therefore falls well below the proposals which NICE is currently consulting on in relation to the appraisal system for medicines at the end of life. We would hope that the Committee is minded of this consultation and considers the proposal outlined in it when making its final recommendations. 5.3 As a charity dealing with patients and their families being denied treatment for myeloma, we are more than disappointed that the committee is minded to reject this treatment which is important to patients. We believe that this treatment should be made available to those that would benefit from it, on the basis of clinical decision making, rather than on purely cost-effectiveness grounds.	The manufacturer proposed a patient access scheme that was considered by the Committee in making its recommendations. The Committee considered the Institute's supplementary advice to Appraisal Committees on end of life treatments in making its final recommendations for lenalidomide. Comment noted. NICE is required to consider the cost effectiveness of treatments.
PCT	Do you consider that all of the relevant evidence has been taken into account? Yes, we think that you have considered all the relevant evidence that is available in the public domain.	Comments noted.
PCT	Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence,	Comments noted

Consultee	Comment	Response
	and that the preliminary views on the resource impact and implications for the NHS are appropriate? Yes, we think that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	
PCT	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? Yes, we consider that the provisional recommendations of the Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted
PCT	Are there any equality related issues that need special consideration that are not covered in the ACD? No, we are not aware of any issues that need special consideration.	Comments noted
PCT	Specific comments • We concur with the conclusions of the draft appraisal. • We agree that multiple myeloma is an incurable disease and that lenalidomide is a clinically effective medicine for this condition. • 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 multiple myeloma patients. • We are also concerned that if a patient is started on lenalidomide, it is unclear for how long it will 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). It will be also useful to define any sub group of patients that may benefit more than others (if appropriate). • We think that the RCTs of lenalidomide do not have appropriate comparator such as thalidomide or bortezomib and that the high degree of crossover	Comments noted. Lenalidomide is administered until disease progression or the occurrence of unacceptable side effects. The patient access scheme proposed by the manufacturer means the manufacturer pays for cost of lenalidomide for people who have not progressed after 26 cycles (normally 2 years). 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) 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). Lenalidomide is recommended for the subgroup of people who have had two or more prior therapies. A revised estimate of cost effectiveness submitted by the manufacturer incorporated the costs of thromboprophylaxis (see FAD 3.19 and 4.15).

Consultee	Comment	Response
	(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. • Thromboprophylaxis (such as low molecular weight heparin or warfarin) is recommended in patients receiving lenalidomide, who have additional risks for thrombosis. • Sandwell PCT has received individual funding requests for lenalidomide in multiple myeloma and after appraising the published literature/evidence, we came to similar conclusions, i.e. 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. • We are not in a position to comment on technical details of the economic analysis.	
RCN	No Comments	
DH	No Comments	
WAG	No Comments	

Comments received from commentators

Commentator	Comment	Response
Janssen-Cilag	**i) Do you consider that all of the relevant evidence has been taken into account?** We consider that the relevant published evidence to date has been taken into account; in addition we would like to recommend the consideration of the study by Dimopoulos et al. to be published/ presented on December 6th 2008 at the American Society of Hematology Meeting.	Comments noted.

Commentator	Comment	Response
	ii) 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 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 **iii) 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?** We consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS **iv) Are there any equality related issues that need special consideration that are not covered in the ACD?** No comment	
Janssen-Cilag	The ACD states page 5 under section 3.1: 'For people in whom bortezomib was contraindicated, for people who had received more than one prior therapy and for people who had received prior thalidomide (only one or more than one prior therapy) the comparator was dexamethasone' It is understood 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 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 paragraph referred to in the comment is a description of the model submitted by the manufacturer. For full details of contraindications a reference is made to the SPC (FAD 2.2). The Committee also noted that for people with peripheral neuropathy the use of bortezomib was 'restricted' and not 'contraindicated' (FAD 4.7).
Janssen-Cilag	The ACD states page 14 under section 4.6: 'It heard from clinical specialists and patient experts that lenalidomide was particularly useful for people with pre-existing peripheral neuropathy in whom the	Comment noted. Please see above.

Commentator	Comment	Response
	use of bortezomib at first relapse was 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. - 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 (please see paragraph below), 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 Under the Peripheral Neuropathy section the SPC* states: ‘Treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Improvement in, or resolution of, peripheral neuropathy was reported in 51% of patients with Grade 2 peripheral neuropathy in the single agent phase III multiple myeloma study and 71% of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase II studies, respectively. In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.’	

Commentator	Comment	Response

Summary of comments received from members of the public

Theme	Response
Lenalidomide is of proven clinical effectiveness and well tolerated with few adverse effects. It is an oral drug that saves on administration costs and helps patients live independent lives	The Committee accepted that the clinical effectiveness of lenalidomide in combination with dexamethasone compared with dexamethasone alone has been shown (see FAD 4.5).
Denying patients access to a drug based on cost when it is of proven efficacy is unacceptable. The knowledge of an effective treatment which they are not able to access will be difficult for patients to bear	The Appraisal Committee is required to make decisions on the basis of both clinical and cost effectiveness (see Guide to the methods of technology appraisals http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf, section 6.2).
Multiple myeloma is a rarer disease which therefore costs more to treat – patients should not be penalised for it especially as it is not a lifestyle disease.	The Appraisal Committee the Institute's supplementary advice to Appraisal Committees on end of life treatments in making its recommendations and one aspect of this was the estimated size of the eligible population (see FAD 4.17).
It is unfair to deny people drugs when they have paid their taxes in to the system, often for many years, and expected that they would have access to life saving medications. This is an unfair, unjust and immoral decision that goes against the principles of the NHS	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. For further details, please see the Guide to the Methods of Technology Appraisal http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
NICE, the manufacturer and the NHS should work together to negotiate a price for the drug. They need to reach a compromise on a negotiated procurement scheme and a risk sharing arrangement such as for Velcade.	The Appraisal Committee made recommendations incorporating the patient access scheme proposed by the manufacturer.

Theme	Response
Lenalidomide needs to be retained as a therapeutic option for the management of multiple myeloma. NICE should not restrict the choice of treatments available at each line and should retain the option to retry treatment with which a good response was obtained, at subsequent relapses. This will give doctors the flexibility required to exercise their clinical judgement. It is especially required in patients with neuropathy.	The Institute's was given a remit to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications, and the circumstances in which it was found to be clinically and cost effective were as an option for the treatment of people who have had two or more prior therapies when used in accordance with a patient access scheme.
The dose of lenalidomide is frequently reduced in clinical practice and this leads to reduction in costs.	Dose reduction was accounted for in the cost effectiveness analysis.
The evidence considered in the appraisal is already outdated. There is evidence for the efficacy of other combination therapies that are superior to bortezomib and dexamethasone.	The appraisal will be considered for review along with the guidance for bortezomib in 2010 (see FAD 7.2).
The topic must be reviewed sooner than in three years time. This is due to the availability of new evidence and also because patients refused this treatment would die before the recommendations are reviewed.	The appraisal will be considered for review along with the guidance for bortezomib in 2010 (see FAD 7.2).
Lenalidomide will allow patients to live longer and they may benefit from future innovations in the treatment of multiple myeloma that may occur during this extended life.	Comment noted
Given the cost of lenalidomide, very few people are going to be able to afford it to 'top-up' their care.	Comment noted
Lenalidomide is available to people with multiple myeloma in other EU and North American countries.	Comment noted
Younger patients are not represented in the trial data. Younger patients have potentially more to gain than the average of patients in the clinical trial and this has not been acknowledged in the economic modelling. The QALY is an average and not a measure of individual benefit. The average QALY gain does not represent that for an individual patient. Younger patients may have families with young children and the QALY does not capture the benefit of a longer life for a parent.	Comment noted. 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 analyses; this was chosen as most appropriate for the Appraisal Committee's purpose. For details of the reference-case method for measuring and valuing health effects, see section 5.4 of the Guide to the Methods of Technology Appraisal.

Theme	Response
The wide spread use of lenalidomide should lead to a decrease in cost due to economies of scale	Comment noted. The cost of lenalidomide in the appraisal is the list price. For the treatment of people who have had two or more prior therapies in whom lenalidomide is recommended, a patient access scheme applies by which the cost of lenalidomide is met by the manufacturer after 26 cycles (normally 2 years). There is no reduction in cost of lenalidomide on the basis of how widely it is used.
Money is wasted in the NHS on bureaucracy and administration. The NHS could be made more efficient and save money to be spent on drugs for cancer like lenalidomide. The government is able to find money to bail out banks and financial institutions – why can they not find money for cancer drugs? The government should also fund drug research – this will decrease the cost to manufacturers of developing drugs and lead to cheaper products	Comments noted. The remit of the appraisal is to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications for multiple myeloma. Appraising the cost effectiveness of technologies is one way to inform more efficient spending of NHS resources. The perspective of NICE appraisals on costs is that of the NHS and Personal Social Services (see the Guide to the Methods of Technology Appraisal).
The subgroup of people who have had thalidomide consists of people who become resistant to thalidomide and have stopped the drug and people who stopped thalidomide due to toxicity. Given the similarity of lenalidomide it is unlikely to be effective in people with resistance to thalidomide but is likely to remain effective in people who develop toxicity to thalidomide. The drug should be approved for this latter group as it is likely to be cost effective.	Comment noted. The recommendations in the FAD for the use of lenalidomide for people who have received two or more prior therapies includes those who have received prior thalidomide.
Lenalidomide should remain a trial drug until further data on side effects is obtained from NHS funded drug trials.	Lenalidomide has a marketing authorisation, and the remit of the appraisal is to appraise the clinical and cost effectiveness of lenalidomide within its licensed indications for multiple myeloma. The Committee concluded that lenalidomide should be recommended as an option for the treatment of people who have had two or more prior therapies under the conditions of the patient access scheme proposed by the manufacturer where the drug cost to the NHS is capped at 26 cycles (normally 2 years) of treatment.