NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to:

- clarify its rationale for the appropriate comparators for lenalidomide plus dexamethasone (len/dex) that are used in routine clinical practice, and provide evidence to support the statement that other 'conventional' therapies are not superior to dexamethasone monotherapy

- provide an analysis comparing len/dex with bortezomib using the continuation rules and response-based rebate scheme recommended in NICE technology appraisal guidance 129 ('Bortezomib monotherapy for relapsed multiple myeloma'; available from www.nice.org.uk/TA129)

- provide a model which could run the probabilistic sensitivity analysis

- clarify the random process by which the model creates cohorts from the trial population

- explain the absence of utility decrements associated with adverse effects in the model

- provide evidence to support the assertion that there was no improvement in survival times over the duration of collection of the data from the Medical Research Council (MRC) studies that were used to model post-progression survival

- provide details of the use of granulocyte colony-stimulating factor in the clinical trials and model

- provide details of the predictive performance of the equations used for post-progression survival

- provide data to allow comparison between the population in the clinical trials for lenalidomide and the population in the MRC trials

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- provide details on treatment interruptions and discontinuations in the clinical trials and the incorporation of this aspect into the economic model.

The ERG noted the following errors in the submitted model, which were then corrected by the manufacturer:

- a discrepancy between regression coefficients in the submission and those used in the model for the subgroup of patients with more than one prior therapy

- an incorrect specification in the model spreadsheets that resulted in misclassification of the response level of patients in the subgroups with one prior therapy.

- double counting of the progression-free survival time in calculating the overall survival (OS).

This resulted in a final, revised version of the manufacturer's submission dated 13 August 2008.

Licensed indication

Lenalidomide (Revlimid, Celgene) in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

Key issues for consideration

- Are the comparators presented in the manufacturer's submission appropriate for the appraisal?

- What is the most appropriate way to account for crossover between the len/dex and dexamethasone-only arms of the pivotal clinical trials in order to extrapolate overall survival (OS) in the analysis?

- What are the appropriate general medical management (that is, non-drug) costs to be included in the economic modelling?

- What is the Committee's view of the ERG's recalculated incremental cost-effectiveness ratios (ICERs) from the manufacturer's economic model?

- Which are the appropriate subgroups of patients in clinical practice that should be considered in the economic analysis?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients with multiple myeloma who have received at least one prior therapy.
Intervention	Lenalidomide in combination with high-dose dexamethasone.
Comparators	• The principal comparator considered in the submission is monotherapy with high-dose dexamethasone. This is based on data from the registrational trial programme for lenalidomide. • An additional comparison is made with bortezomib monotherapy using indirect methods. The MS states that it is important to consider this comparison as informative only. • A comparison with bortezomib in combination with high-dose dexamethasone was not considered to be appropriate, on the grounds that this combination is not licensed and data are only currently available from phase II studies. • A comparison with thalidomide was not considered. Thalidomide is licensed only for the first-line treatment of multiple myeloma and a marketing authorisation application for thalidomide for relapsing or refractory multiple myeloma was withdrawn. • Other conventional therapies, including repeat initial chemotherapy, were not included on the grounds that they are not superior to dexamethasone monotherapy, in terms of myeloma control and their tolerability profile. In addition, there are no standard regimens in use, but rather a wide variety, making meaningful comparisons difficult.
Outcomes	The outcome measures considered include the following: *Primary efficacy outcome* • time to disease progression *Secondary efficacy outcomes* • OS • response rates • adverse effects of treatment.

1.2   Evidence Review Group comments

1.2.1   Population

The population in the submission, people with multiple myeloma who have received one prior therapy, matches the licensed indication for lenalidomide.

1.2.2   Intervention

The intervention, lenalidomide in combination with high-dose dexamethasone, was as per the scope and the licensed indication.

1.2.3   Comparators

The comparators used in the submission were high-dose dexamethasone and bortezomib monotherapy. Other comparators outlined in the scope were not included. Expert opinion suggests that bortezomib in combination with dexamethasone may be standard clinical practice, and that thalidomide-containing regimens may also be used in clinical practice. The manufacturer clarified the absence of evidence for the use of thalidomide as second-line therapy. A systematic review did not produce evidence for the comparative efficacy of repeat initial therapy (including melphalan, vincristine, cyclophosphamide and doxorubicin) or other comparators and dexamethasone as second-line therapy.

1.2.4   Outcomes

The ERG agreed that the outcomes were appropriate and clinically meaningful.

1.2.5   Economic evaluation

The ERG agreed that the 30-year time horizon was effectively a lifetime analysis.

1.2.6 Subgroups

The following subgroups were considered in the analysis:

Table 1: Subgroups and comparators

Patient subgroup	Treatments
One prior therapy only	Len/Dex *v.* bortezomib
One prior therapy only and have pre-existing peripheral neuropathy	Len/Dex *v.* Dex
At least two prior therapies	Len/Dex *v.* Dex
Prior treatment with thalidomide (1 prior therapy only)	Len/Dex *v.* Dex
Prior treatment with thalidomide (2 or more therapies)	Len/Dex *v..* Dex

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The MS identifies two randomised controlled trials (RCTs) (MM-009 and MM-010) of identical design that examine treatment with lenalidomide plus dexamethasone (len/dex) for patients with multiple myeloma who have received one prior therapy. The trials enrolled 353 and 351 patients respectively (n = 704). Patients were stratified according to their serum level of β2-microglobulin, previous stem cell transplantation and number of previous antimyeloma therapies. Patients in the treatment arm received lenalidomide plus pulsed high-dose dexamethasone in 28-day cycles. Patients in the control arm received dexamethasone only. Treatment was continued until disease progression or the occurrence of unacceptable side effects. The primary outcome was time to progression (TTP). Secondary outcomes were OS, response rates, safety and time to decrease of performance status. Response was assessed using the EBMT criteria (see table 4 on page 29 of the ERG report). Additionally, a number of post-hoc subgroups were investigated from the pooled populations. These included patients with pre-existing peripheral neuropathy and patients who had received prior

thalidomide or bortezomib therapy. At progression or unblinding, patients in the dexamethasone monotherapy group were allowed to receive lenalidomide.

The median TTP in each study was calculated at unblinding (median follow-up 17.1 and 16.7 months in the two studies).The median TTP at unblinding for each trial and the pooled results are given in table 1.

Table 2: Time to progression (TTP)

| | MM-009 | | MM-010 | | Pooled | |
	Len/dex	Dex	Len/dex	Dex	Len/dex	Dex
n	177	176	176	175	353	351
Median TTP (weeks) [95% CI]	48.1 [36.9, 61.4]	20.1 [16.7, 23.1]	48.7 [40.9, 72.1]	20.1 [18.1, 20.7]	48.3 [41.1, 60.1]	20.1 [19.9, 20.7]
HR [95% CI]	0.354 [0.270, 0.466]		0.351 [0.266, 0.463]		0.35 [0.29, 0.43]	
Log-rank P-value	< 0.001		< 0.001		< 0.001	
Abbreviations: Len/dex, lenalidomide plus dexamethasone; HR, hazard ratio; CI, confidence interval.						

Median overall survival was analysed at various time points. The results at unblinding (May 2006), 3 years 3 months and 2 years 8 months after study initiation for each trial respectively are shown in table 2. The pooled results in table 2 are updated results from January 2007 (with a combined median follow-up time of 31.3 months).

Table 3: Overall survival (OS)

| | MM-009 | | MM-010 | | Pooled | |
	Len/dex	Dex	Len/dex	Dex	Len/dex	Dex
n	177	176	176	175	353	351
Median OS (months)	29.6	20.2	NE	20.6	■	■
Hazard ratio [95% CI]	0.44 [0.30, 0.65]		0.66 [0.45, 0.96]		■	
Log-rank test P-value	<0.001		0.03		0.015	
Abbreviations: Len/dex, lenalidomide plus dexamethasone; CI, confidence interval.						

The response to therapy at unblinding (median follow-up 17.6 and 16.4 months) for each trial and the pooled results are given in table 3.

Table 4: Response rates

	MM-009		MM-010		Pooled	
	Len/dex	Dex	Len/dex	Dex	Len/dex	Dex
n	177	176	176	175	353	351
Response						
Complete response (CR)	25 (14.1%)	1 (0.6%)	28 (15.9%)	6 (3.4%)	53 (15.0%)	7 (2.0%)
Near-complete response (nCR)	18 (10.2%)	2 (1.1%)	15 (8.5%)	3 (1.7%)	33 (9.3%)	5 (1.4%)
Partial response (PR)	65 (36.7%)	32 (18.2%)	63 (35.8%)	33 (18.9%)	128 (36.3%)	65 (18.5%)
Stable disease (SD)	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)	107 (30.3%)	199 (56.7%)
Progressive disease (PD)	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)	8 (2.3%)	50 (14.2%)
Response not evaluable (NE)	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)	24 (6.8%)	25 (7.1%)
P-value	< 0.001		< 0.001		< 0.001	
Dichotomised response						
CR, nCR or PR	108 (61.0%)	35 (19.9%)	106 (60.2%)	42 (24.0%)	214 (60.6%)	77 (21.9%)
SD, PD or NE	69 (39.0%)	141 (80.1%)	70 (39.8%)	133 (76.0%)	139 (39.4%)	274 (78.1%)
Odds ratio [95% CI]	6.31 [3.91, 10.17]		4.80 [3.03, 7.59]		5.48 [3.94, 7.63]	
P-value	< 0.001		< 0.001		< 0.001	

Abbreviations: Len/dex, lenalidomide plus dexamethasone; CI, confidence interval.

Subgroup analysis was performed on the pooled data. There was no evidence to suggest that the relative efficacy of the len/dex combination differed from that of dexamethasone alone in any of the post hoc subgroups including impaired renal function, IgA status, elderly and prior thalidomide or bortezomib therapy. The outcomes in the trials for the subgroups with one prior therapy and more than one prior therapy can be found in the ERG report (for TTP in tables 6 and 7 on page 36, for OS in tables 11 and 12 on pages 41–42, and for response rates in tables 14 and 15 on page 44).

The results for OS are affected by crossover of patients at unblinding: 170 of 350 patients opted to receive lenalidomide on disease progression or at unblinding. However, these patients were analysed as remaining in the

dexamethasone arm. A similar confounding applies to TTP, but to a lesser degree as most patients (over 75%) had progressed at unblinding.

In addition to pooling, a meta-analysis was performed to combine the results of the trials. This resulted in a median difference in TTP of 28.24 weeks (95% confidence interval [CI] 18.39–38.08) and an odds ratio for OS of 1.44 (95% CI 1.34–1.56). There was no evidence of heterogeneity between the trials.

An indirect comparison was undertaken to compare len/dex with bortezomib monotherapy, as there were no head-to-head trials. The results of the trials for len/dex were compared with the results of the APEX trial for bortezomib. For median TTP, len/dex had a 34-week advantage over bortezomib for people who had one prior therapy, and there were no significant differences for the secondary outcomes of complete response, partial response and progressive disease. However, the MS states that this analysis is limited by the low number of data points. In addition, the common comparator, dexamethasone, was an active treatment and was not used in the same dose across the trials, and there were differences between the trials in the definition of response.

The commonest adverse effects associated with the use of lenalidomide were haematological, including anaemia, neutropenia and thrombocytopenia. These were the primary reasons for dose reductions, but they necessitated discontinuation of therapy only infrequently. The incidence of complications of these adverse effects was low. Other adverse effects include cardiac adverse events, fatigue, pneumonia and hyperglycaemia. Lenalidomide was associated with an increased risk of venous thromboembolism. The risk was associated with the concomitant use of erythropoietin, as well as with a previous history of thrombosis, older age and lower baseline plasma cell count. The EMEA recommended further monitoring for this adverse effect, careful observation of patients, avoidance of concomitant use of other agents that increase the risk of thrombosis and the use of prophylactic anti-thrombotic medications (heparin, warfarin) in patients with risk factors[1].

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2.2 Evidence Review Group comments

The ERG was satisfied that the search conducted for the MS had not missed any relevant trials. The trials were, in general, well conducted. The population in the trials was representative of patients in routine clinical practice in the UK. The major concern was that the crossover of patients between the treatment and comparator arms on disease progression or unblinding would lead to an underestimation of the efficacy of the intervention, with OS being affected more than TTP.

The ERG agreed that the choice of outcomes in the trials was appropriate. It noted that the complete response rates (and TTP) have not been found to be valid surrogates for OS in evidence assessing first-line therapy for multiple myeloma.

The meta-analysis in the MS provided estimates for OS using the proportion of patients alive in the trial arms at the date of analysis and an odds ratio for the same, as well as the difference in median TTP for the two arms. The ERG considered that dichotomised survival proportions and median survival times were unreliable, and presented a meta-analysis based on combining hazard ratios. The ERG repeated the meta-analysis for hazard ratios for TTP and OS, and the results are shown in table 4.

Table 5: ERG's meta-analysis of trials

Outcome	P (het.)	Fixed-effects model			Random-effects model		
		HR	95%CI	P (HR=0)	HR	95%CI	P (HR=0)
TTP	0.960	0.353	(0.290, 0.428)	<0.001	0.353	(0.290, 0.428)	<0.001
OS	0.142	0.541	(0.413, 0.709)	<0.001	0.540	(0.363, 0.803)	0.002

Abbreviations: TTP, time to progression; OS, overall survival; HR, hazard ratio; CI, confidence interval; het.:heterogeneity.

Similarly, the ERG considered the mixed treatment comparison of len/dex with bortezomib to be incorrect because of the use of median survival time and the

inappropriate use of assumed standard errors. The ERG performed a mixed treatment comparison based on hazard ratios (see table 5).

Table 6: Results of the ERG's mixed treatment comparison

Comparison	Input data	HR (95% CI)
Len/dex vs bortezomib	[indirect comparison]	0.557 (0.337, 0.912)
Len/dex vs dex	MM-009: HR 0.311; SE (ln HR) 0.234 MM 010: HR 0.312; SE (ln HR) 0.266	0.312 (0.220, 0.438)
Bortezomib vs dex	HR: 0.56; SE (ln HR): 0.186	0.558 (0.388, 0.804)
Abbreviations: Len/dex, lenalidomide plus dexamethasone; HR, hazard ratio; CI, confidence interval; SE, standard error.		

On reviewing the results, the ERG commented that while the median TTP is similar in both arms of the trials in subgroups of patients with one or more prior therapies, the relative benefit of len/dex was greater in the group with one prior therapy in both trials. A similar benefit was seen across all subgroups.

2.3 Statements from professional/patient groups and nominated experts

Consultees stressed the importance of lenalidomide, as people with multiple myeloma have a poor prognosis. It has a tolerable side-effect profile and is administered orally, thereby avoiding hospital visits. It would be particularly useful for patients who have experienced peripheral neuropathy, as a result of either the disease or the treatment, as this is a significant cause of morbidity. It was noted that lenalidomide increases the risk of venous thromboembolism and that patients with other risk factors had to be given concomitant anticoagulant prophylaxis. The importance of having a choice of various treatments for individualised care was also stressed, as the natural history of multiple myeloma is unpredictable.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

A systematic search for economic evaluations of lenalidomide identified two studies. One study was in a Scottish setting and the other was in a Welsh setting. Both were based on the pivotal trials (the MM-009 and MM-010 RCTs described in section 2.1) and used a discrete-event simulation model. In the Scottish setting len/dex was calculated to have an ICER of £35,673 per QALY gained over a lifetime time horizon. In the Welsh setting the ICER for the group with one prior therapy was £34,770 per QALY gained, and that for the group with more than one prior therapy was £30,871 per QALY gained over a lifetime time horizon.

The economic evaluation in the MS used a discrete-event simulation model. This model uses two separate prediction equations, based on patient characteristics and treatment, to calculate TTP and post-progression survival, then adding both together for OS. A cohort is created by randomly sampling (with replacement) patients from the pooled trial populations. For subgroups within the model the cohort is created from the relevant population. Each patient in the cohort has an individual profile of characteristics, which is then linked to the outcome observed for that patient in the trial. The model runs multiple cohorts to obtain an average result. The MS states that this allows the model to capture the variability within individuals in the trial and allows correlation between observed parameters to be retained within the model.

The model divides patients from both arms of both trials into four groups according to their level of response. In building a cohort for the study population or any of the subgroups, the model ensures that the proportion of patients achieving a particular response in the trial is replicated in the cohort. To calculate TTP, the model uses observed TTP if progression occurred within the duration of follow-up and the patient was assigned to the same treatment group in the model as in the trial. Where a patient's disease had not

progressed in the trial, or where progression had occurred but the patient was in a different patient group in the model compared with the trial, TTP was calculated using an equation that assumes a Weibull distribution and has patient characteristics, treatment response and treatment as independent variables.

For bortezomib, the response rates are taken from the APEX trial and the equation for TTP is calibrated such that the median TTP is the same as that within the trial.

The equation for post-progression survival is assumed to take the exponential form. As the trial results are confounded by the crossover of patients, this equation is therefore calibrated by adding a factor so that the observed survival with dexamethasone post-progression is equal to that observed in UK Medical Research Council (MRC) trials, which represent a large group of UK patients with multiple myeloma and their outcomes[2]. This assumes that the survival experience of this cohort is the same with dexamethasone as with other regimens. The MS also states that despite the historical nature of the MRC data and survival experience, there was no trend to improved survival over the 30 years during which the data were collected and therefore the survival experience of the patients in the pivotal trials could be predicted by using this patient cohort from the MRC trials. To do this, the patient profiles for the pivotal trials were applied to the predictors in the survival equations derived from the MRC trial data. This resulted in a higher median survival with dexamethasone for the patients than was observed in the MRC trials (███████████████████████████ for patients with one and more than one prior therapy respectively). The MS stated that this makes the analysis conservative.

The model considers subgroups of patients who have received one prior therapy (with this group divided further into those who do and do not have peripheral neuropathy), patients who have received two or more prior therapies, and patients who have received thalidomide. For patients with one

prior therapy len/dex was compared with bortezomib monotherapy. For patients with peripheral neuropathy and for patients with two or more prior therapies, the comparator was dexamethasone alone.

There were no measurements of health-related quality of life in the pivotal trials. The utility values were based on a study evaluating intensive chemotherapy followed by myeloablation and autologous stem cell transplantation in patients with multiple myeloma. Utility values were collected using the EQ-5D questionnaire. For the complete response, partial response and stable disease states, a utility value of 0.81 (the utility value of the general public at age 54) was used. A utility value of 0.64 was applied to the progressive disease state. This assumption favours the comparator, as there were more patients in the complete response and partial response states in the len/dex arm. After 2 years a utility value of 0.77 was applied to those whose disease had not progressed.

Only grade 3 and 4 adverse effects were included in the model. Utility decrements for adverse effects were not included. Resource use associated with adverse effects, routine follow-up and laboratory tests (etc.) were collected to build up a profile of resource use for patients depending on disease state and treatment. Resource use profiles were developed for patients during relapse and/or on treatment, and patients in remission on maintenance therapy or off therapy. Resource use was estimated by interviewing 15 specialists across England and Wales who specialised in the management of multiple myeloma.

The results from the model are summarised in table 7.

Table 7: Results submitted by the manufacturer (corrected model)

	1 prior therapy			>1 prior therapy		1 prior therapy (thalidomide)		>1 prior therapy (thalidomide)	
	Len/dex	Bortezomib	Dex	Len/dex	Dex	Len/dex	Dex	Len/dex	Dex
Clinical outcomes									
Time to progression (years) (median, undiscounted)	1.17	0.56	0.39	0.80	0.39	1.57	0.40	0.66	0.34
QALYs (discounted)	■	■	1.53	3.23	0.77	4.49	1.43	2.96	0.70
Life years (mean, discounted)	■	■	2.20	4.76	1.05	6.58	2.10	4.43	1.01
Average total cost (£ discounted, per patient)	■	■	1,366	61,171	694	119,676	1,311	51,745	694
Medication	■	■	109	57,921	109	115,775	107	48,622	106
Monitoring	■	■	1,072	2,504	404	3,149	1,017	2,377	412
Adverse effects/complications	■	■	185	746	181	752	187	746	176
Incremental cost per QALY of len/dex versus:		■	46,865	24,584		38,861		22,589	
Incremental cost per life year of len/dex versus:		■	32,501	16,301		26,421		14,927	
Probability that len/dex is cost-effective (willingness to pay £30,000 per QALY)		■	0%	Approx. 90%		Approx. 5%		100%	

Univariate sensitivity analyses were conducted to explore the impact of:

- changing the costs of adverse effects and disease monitoring

- changing the cost of lenalidomide

- changing the assumed utility scores

- using different utility scores depending on level of response

- reclassifying patients who were not evaluable as being in the stable disease category

- recalibrating the equation for post-progression survival to increase or decrease the median by 1 month.

Multivariate scenarios, with decreases in the cost of lenalidomide and changes in assumed utility, were undertaken as well as the probabilistic sensitivity analysis.

In the sensitivity analysis the base-case results were not changed significantly by changing the resource use as estimated by experts, changing the costs of laboratory tests, decreasing the cost of lenalidomide by 5%, increasing or decreasing the utility scores by 10% or reclassifying patients into the stable disease category. The results were also not sensitive to the recalibration of post-progression survival using data from the MRC trials, or to increasing or decreasing median OS by 1 month.

3.2 Evidence Review Group comments

The ERG accepted the modelling approach used in the MS but did not feel that the extra complexity was justified or necessary. This is because the post-progression courses of individual patients are not tracked in the model and the uncertainty associated with OS is not addressed by the discrete-event simulation model. The ERG accepted the 30-year time horizon as effectively representing a lifetime analysis. However, given the comparatively brief duration of the trial, this introduces considerable uncertainty into the estimates.

The ERG considered that an important comparator, bortezomib plus dexamethasone, was not included within the model. Expert opinion suggested that this combination is routinely used in UK clinical practice. In addition, the comparison with bortezomib in the analysis does not take account of stopping rules as recommended by NICE in its guidance on the use of bortezomib for multiple myeloma (NICE technology appraisal guidance 129: 'Bortezomib monotherapy for relapsed multiple myeloma'). The ERG also noted that the equation used to calculate TTP has a term for treatment allocation to lenalidomide, but not for the comparators.

The ERG expressed several concerns with the use of the clinical effectiveness data in the model. First, the modelled OS for len/dex is better than that observed in the trials. The modelled OS for the dexamethasone group is lower than in the trial because of adjustments using data from the

MRC trials (to take account of the crossover effect in the trial data). However, the modelled OS for len/dex is higher than in the RCTs. The exact discrepancy varies between subgroups and is greatest in the group with one prior therapy; this improves the cost effectiveness of len/dex. When the modelled OS is adjusted to fit the len/dex OS in the RCTs, the ICER for the group with one prior therapy for len/dex compared with bortezomib increases to ▮▮▮▮▮▮ per QALY gained and that for len/dex compared with dexamethasone increases to £69,500 per QALY gained. The ERG notes that the group with one prior therapy and its subgroup with peripheral neuropathy use the same efficacy data but different comparators because there are too few patients in the trial with this adverse effect. For the subgroup with more than prior therapy the ICER increases to £32,900 per QALY gained, and for the thalidomide-treated subgroups the ICERs are £56,500 per QALY gained for the subgroup with one prior treatment and £30,800 per QALY gained for subgroup with more than prior therapy.

In the case of the modelled TTP, the ERG noted that for both arms it is reasonably consistent with the observed trial results. The modelled TTP is in fact slightly lower than that in the RCTs. This would decrease the cost effectiveness of the intervention, as a longer TTP is associated with higher drug costs. The ERG calculated that adjusting the model TTPs to match the trial values increases the ICER by £1000–2000 depending on whether the figures in the MS or the RCTs are used. The reason for the discrepancy is possibly that 49 patients from the trial were not in the patient files on which the model simulation is based. The patient-level data in the model are also less mature than data in the MS or the RCTs (25.5 months, compared with an RCT follow-up of 33 months and an MS follow-up of 40 months). The ERG was concerned that overall biases in the data input in the model are likely to affect model's ability to simulate the trial, and therefore that the predicted model results are unlikely to be accurate.

The ERG considered the approach used in the MS to extrapolate OS beyond that recorded in the trial and the adjustment made to allow for the crossover effect in the trial data. A factor was added to the post-progression equation for the dexamethasone arm to calibrate estimated OS with that observed in the UK MRC multiple myeloma trials, with the effectiveness of dexamethasone in the MRC trials adjusted according to the patient characteristics in the RCTs. The use of historical data limits the accuracy of the model, as previous survival experience may not always accurately predict current and future outcomes. The ERG considered this to be important, as the approach to estimating OS had a substantial impact on the estimates of cost effectiveness. The ERG suggested matching the mean (rather than the median) OS of patients on dexamethasone in the post-progression arm to the mean survival of patients treated with dexamethasone in the MRC trials. This is because the ICER is a ratio of means, and the use of medians ignores the shape of the survival curve tail beyond the 50th percentile. The exponential model used was a poor fit to the observed OS. When the analysis is carried out in this manner, the ICER for len/dex for the subgroup with one prior therapy increases marginally. However, the ICER for the subgroup with more than one prior therapy increases to £33,200 per QALY gained, and that for the thalidomide-exposed subgroup with more than one prior therapy increases to £30,200 per QALY gained.

The ERG also stated that the costs associated with the administration of intravenous bortezomib are overestimated in the analysis (£1628 rather than £432). The administration costs are also higher than those considered reasonable in the previous NICE appraisal of bortezomib (NICE technology appraisal guidance 129). Using the lower cost for the administration of bortezomib, the ICER for len/dex for the group with one prior therapy increases to ▮▮▮▮ per QALY gained. The MS also assumes a maximum of 8 cycles of bortezomib, whereas there was a maximum of 11 cycles in the trial. Correcting this decreases the ICER for len/dex compared with bortezomib to ▮▮▮▮ per QALY gained. The model allows for variation in the dose intensity

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of lenalidomide to take account of the treatment reductions and interruptions observed in the trial. However, the dose intensity of bortezomib is assumed to be 100%, which does not take account of discontinuation or suspension of treatment.

The approach to costs in the analysis raised a number of concerns. The ERG noted that the costs for outpatient appointments for people in the states of progression-free survival and post progression are not included in the model. Including these costs increases all ICERs slightly. The ERG also thought that the costs for medical management in the model (other than the drugs) are lower than those used in the appraisal of bortezomib (technology appraisal guidance 129). Assuming a higher cost for management from the previous appraisal suitable adjusted for inflation (£551 per month rather than £111 per month for progression-free survival and £149 per month for progressive disease) increases the ICERs for all subgroups.

The model does not include the disutility for adverse effects. As these were greater in the len/dex group, the analysis would be biased towards lenalidomide. In addition, no adverse effects were extrapolated after 2 years, and the use of granulocyte colony-stimulating factor for the treatment of haematological side effects of lenalidomide was not costed.

The model used the same utility value for the disease states of complete response, partial response and stable disease. The ERG suggested that this may not be conservative, as expert opinion suggests a minimal difference in utility level between responses states. In the analysis the utility value for progression-free survival was that of the general population of comparable age. However, progression-free survival is likely to be associated with a lower health-related quality of life than that of the general population. The assumed level for utility in the progression-free survival state has little impact on ICERs, as patients spend a comparatively longer time in the post-progression state. The ERG conducted a re-analysis assuming a 10% lower utility for both states

(progressive disease and progression-free survival) than that used in the MS. This had the effect of increasing all ICERs.

Further analyses conducted by the ERG using the submitted model included:

- adjusting the OS for patients treated with len/dex in the model so that it more accurately predicted median OS observed in the trial

- adjusting the model so that the predicted median time to progression (TTP) for len/dex more closely approximated the trial results

- adjusting the post-progression survival equations for dexamethasone such that the mean (rather than median) OS matches that in the MRC data

- recalculating the costs associated with the administration of bortezomib

- assuming a maximum of 11 (rather than 8) cycles of treatment with bortezomib

- recalculating the costs associated with the medical management of multiple myeloma using costs taken from NICE technology appraisal guidance 129

- using lower estimates of utility values associated with the progression-free and progressive disease states.

Table 8 summarises of the changes to the base-case ICERs resulting from the re-analyses by the ERG.

Table 8: Results of the ERG re-analysis

Analysis	ICER (£ per QALY gained)				
	1 prior therapy len/dex vs dex	1 prior therapy len/dex vs bortezomib	>1 prior therapy len/dex vs dex	1 prior therapy (thalidomide) len/dex vs dex	>1 prior therapy (thalidomide) len/dex vs dex
Celgene base case	£46,900	▮▮▮▮	£24,600	£38,900	£22,600
Improved fit to len/dex OS	£69,500	▮▮▮▮▮	£32,900	£56,500	£30,800
Dex mean OS (not median) adjusted to results of MRC trials	-		£33,200		£30,200
Max 11 bortezomib cycles (rather than 8)	-	▮▮▮	-	-	-
Bortezomib administration costs decreased	-	▮▮▮	-	-	-
Medical management costs taken from bortezomib appraisal	£55,900	▮▮▮	£33,900	£47,600	£31,500
Other re-analyses that increase all ICERs were: comparison with bortezomib/dex instead of monotherapy; taking account of the bortezomib response-rebate scheme; adjusted utility to account for adverse effects; reducing bortezomib dose intensity.					

4   Authors

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Ashcroft and Fergus Gleeson.

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A   The evidence review group (ERG) report for this appraisal was prepared by the Peninsula Technology Assessment Group:

- Hoyle M, Rogers G, Garside R et al, The clinical and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene, September 2008.

B   Submissions or statements from the following organisations:

I   Manufacturer/sponsor

- Celgene

II   Professional/specialist, patient/carer and other groups:

- British Society for Haematology
- Myeloma UK
- UK Myeloma Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

C   Additional references used:

1. Anon., (2007) EMEA: Scientific discussion: Revlimid. Available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/revlimid/H-717-en6.pdf. Accessed September 2008.

2. Drayson MT, Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, et al. Survival from relapse and the influence of therapy. Haematologica/The Hematology Journal: XIth International Myeloma Workshop Proceedings 2007;92(6, s2):173-, Abstract # PO-665