NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

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

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies, with the following condition:

- The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.

1.2 People currently receiving lenalidomide for the treatment of multiple myeloma, but who have not received two or more prior therapies, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Lenalidomide (Revlimid, Celgene) is an immunomodulating agent. It belongs to a class of agents often referred to as immunomodulatory derivatives, which are all structural derivatives of thalidomide. The exact mechanism of action of lenalidomide is not understood but it has anti-neoplastic, anti-angiogenic and pro-erythropoietic properties. Lenalidomide in combination with dexamethasone is licensed for the treatment of multiple myeloma in patients who have received at least one prior therapy. The recommended starting dose of lenalidomide for adults over 18 years is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. Treatment with lenalidomide is continued until disease progression or unacceptable adverse effects occur. For full details, see the summary of product characteristics.

2.2 The most serious adverse effects of lenalidomide treatment are grade 4 neutropenia and venous thromboembolism. The most

frequently observed adverse effects, which occurred significantly more frequently in the lenalidomide/dexamethasone group compared with the placebo/dexamethasone group in clinical trials (see section 3), were neutropenia, fatigue, asthenia, constipation, muscle cramp, thrombocytopenia, anaemia, diarrhoea and rash. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis. Pregnancy must be ruled out before starting treatment in women of child-bearing age, and these women must use effective contraception while on lenalidomide. For full details of adverse effects and contraindications, see the summary of product characteristics.

2.3 Lenalidomide 25 mg capsules cost £4368 per 21 capsules (excluding VAT; 'British national formulary' [BNF] edition 55). Dosage is continued or modified based upon clinical and laboratory findings. For example, if lenalidomide is continued for ten 28-day cycles without dose reduction, the cost would be £43,680. The manufacturer of lenalidomide (Celgene) has agreed a patient access scheme with the Department of Health, in which the cost of lenalidomide for people who remain on treatment for more than 26 cycles will be met by the manufacturer. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of lenalidomide and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer produced an analysis of the clinical and cost effectiveness of lenalidomide for the treatment of multiple myeloma

in people who had received at least one prior therapy. This included people at first and subsequent relapse and people who had progressive disease after two or more cycles of anti-myeloma treatment. The trial population was divided into five subgroups for the economic analysis. For people who had received only one prior therapy the main comparator was bortezomib monotherapy, which is currently recommended as a treatment option in 'Bortezomib monotherapy for relapsed multiple myeloma' (NICE technology appraisal guidance 129). For people in whom bortezomib was contraindicated, people who had received two or more prior therapies and people who had received prior thalidomide (only one prior therapy or two or more prior therapies), the comparator was dexamethasone.

3.2 Two randomised controlled trials (RCTs), of identical design but differing in their locations (MM-009 and MM-010), compared treatment with lenalidomide plus dexamethasone (len/dex) with dexamethasone alone for patients with multiple myeloma who had received at least one prior therapy. In both arms, the regimen of dexamethasone was pulsed high-dose dexamethasone in 28-day cycles. The trials enrolled 353 and 351 patients, respectively (n = 704). Patients were stratified according to their serum concentration of β2-microglobulin, previous stem-cell transplantation and number of previous anti-myeloma therapies. Treatment was continued until the disease progressed or unacceptable adverse effects occurred. The primary outcome was time to progression (TTP). Secondary outcomes were overall survival, response rates, adverse effects and time to decrease in performance status. Response was assessed using the European Group for Blood and Marrow Transplantation criteria, and six response categories were defined: complete response, near-complete response, partial response, stable disease, disease progression and 'response not evaluable'. A number of post-hoc

subgroups from the pooled populations were investigated, including patients with pre-existing peripheral neuropathy and patients who had received prior thalidomide or bortezomib therapy. At disease progression or unblinding, patients in the dexamethasone monotherapy group were allowed to receive lenalidomide.

3.3 The median TTP at unblinding from the pooled trials was 48.3 weeks (95% confidence interval [CI] 41.1 to 60.1 weeks) for the len/dex arms and 20.1 weeks (95% CI 19.9 to 20.7 weeks) for the dexamethasone arms. The pooled hazard ratio for TTP was 0.35 (95% CI 0.29 to 0.43; log-rank $p < 0.001$). The median overall survival in one trial, analysed 3 years and 3 months after study initiation, was 29.6 months in the len/dex arm and 20.2 months in the dexamethasone arm (hazard ratio 0.44; 95% CI 0.30 to 0.65; $p < 0.001$). In the second trial, the median overall survival was analysed 2 years and 8 months after study initiation; it could not be estimated in the len/dex arm (because of the number of patients still alive), and was 20.6 months in the dexamethasone arm (hazard ratio 0.66; 95% CI 0.45 to 0.96; $p = 0.03$). For the pooled trials, the subgroup of patients who had received one prior therapy had a median survival of 169.1 weeks in the len/dex arm compared with 145.4 weeks in the dexamethasone arm. For the subgroup of patients who had received two or more prior therapies, the median survival was 144.0 weeks in the len/dex arm compared with 118.0 weeks in the dexamethasone arm. A complete, near-complete or partial response was obtained in 60.6% of patients in the len/dex arms and 21.9% of patients in the dexamethasone arms. The remaining 39.4% of patients in the len/dex arms and 78.1% of patients in the dexamethasone arms had stable or progressive disease, or were not evaluable. The odds ratio for this dichotomised response (complete, near-complete or partial response versus stable disease, progressive disease or response not evaluable) was 5.48 (95% CI 3.94 to 7.63; $p < 0.001$). Over the

course of the first 23 cycles in the trial, about 70% of the treatment days for all patients in the trial were at the full dose of lenalidomide. The dose of lenalidomide was reduced on about 25% of the treatment days, and treatment was interrupted on about 5% of the days.

3.4 The results for overall survival were affected by crossover of patients at unblinding: 170 of 351 patients in the dexamethasone arm opted to receive lenalidomide at disease progression or unblinding. However, these patients were analysed as remaining in the dexamethasone arm. The TTP was also affected by the crossover, but to a lesser degree because most patients (over 75%) had shown disease progression at unblinding.

3.5 In both trials, the differences in TTP and response rates (in favour of len/dex) were observed in all of the prespecified subgroups. The post-hoc subgroups in the trial showed that the efficacy of len/dex relative to dexamethasone alone remained statistically significant in subgroups that had received prior treatment with thalidomide or bortezomib and in subgroups specified by the number of previous therapies for multiple myeloma.

3.6 A meta-analysis was also performed to combine the results of the trials and to confirm the results obtained by the pooling of trials. This resulted in a median difference in TTP of 28.24 weeks (95% CI 18.39 to 38.08 weeks) and an odds ratio for overall survival of 1.44 (95% CI 1.34 to 1.56). The hazard ratio was not calculated. There was no evidence of heterogeneity between the trials.

3.7 An indirect comparison was undertaken to compare len/dex with bortezomib monotherapy because there were no head-to-head trials. The results of the trials for len/dex were compared with the results of the Assessment of Proteasome Inhibition for Extending

Remissions (APEX) RCT. The APEX study compared bortezomib with high-dose dexamethasone. For median TTP, len/dex had a 34-week advantage over bortezomib for people who had received one prior therapy only, and there were no statistically significant differences for the secondary outcomes of complete response, partial response and progressive disease. However, this analysis is limited by the small number of data points. In addition, the common comparator (high-dose dexamethasone) was an active treatment and was not used in the same dose across the trials, and the definition of response differed between the trials.

3.8 The economic evaluation in the manufacturer's submission used a discrete-event simulation model. This model used two separate prediction equations to calculate TTP and post-progression survival values, which were then added together to give overall survival. A cohort was created by randomly sampling (with replacement) patients from the pooled trial populations. For subgroups within the model, the cohort was created from the relevant population. The model attempted to capture the variability between individuals in the trial and to allow correlation between observed parameters to be retained.

3.9 The model divided 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 ensured that the proportion of patients achieving a particular response in the trial was replicated in the cohort. To calculate TTP, the model assumed a Weibull distribution. For bortezomib, the response rates were taken from the APEX trial and the equation for TTP was calibrated such that the median TTP was the same as that within the trial.

3.10 The equation for post-progression survival was assumed to take an exponential form. However, the trial results were affected by the

crossover of patients at unblinding from the dexamethasone arm to receive lenalidomide. Therefore the equation included an adjustment factor that calibrated the modelled median overall survival in the dexamethasone group after progression to be equal to that observed in the UK Medical Research Council (MRC) multiple myeloma trials. This assumed that survival of people with multiple myeloma in this cohort was the same when treated with dexamethasone as with all other regimens used in the MRC trials. The patient profiles from the RCTs in the manufacturer's submission were applied to the predictors in the survival equations derived from the MRC trial data to predict survival in the dexamethasone arm if crossover had not occurred.

3.11 The model considered subgroups of patients who had received one prior therapy (with this group divided further into those who did and did not have peripheral neuropathy), patients who had received two or more prior therapies, and patients who had received thalidomide (divided further into those who had received only one prior therapy and those who had received two or more prior therapies). For patients who had received only one prior therapy, len/dex was compared with bortezomib monotherapy. For patients with peripheral neuropathy and for those who had received two or more prior therapies, the comparator was dexamethasone alone.

3.12 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. For the complete response, partial response and stable disease states, a utility value of 0.81 was used. This value was based on the utility of the general public at an age (median 54 years) corresponding to that of the patients in the study. A utility value of 0.64 was applied to the progressive disease state. After 2 years, a utility value of 0.77 was applied to those patients whose disease had not progressed.

3.13 Only grade 3 and 4 adverse effects were included in the model. Utility decrements for adverse effects were not included. Resource-use data associated with, for example, adverse effects, routine follow-up and laboratory tests were collected to build up a profile of resource use, depending on disease state and treatment. Resource-use profiles were developed for people during relapse and/or on treatment, and for people 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.

3.14 The economic analysis did not produce cost-effectiveness estimates for the whole trial population. In the base case, for the subgroup with one prior therapy, the model resulted in an incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained for lenalidomide that the manufacturer stated was not cost effective compared with bortezomib. For the one prior therapy subgroup, the ICER was £46,865 per QALY gained for lenalidomide compared with dexamethasone. For patients who had received two or more prior therapies the ICER was £24,584 per QALY gained. In the subgroup of patients who had received prior thalidomide, the ICERs were £38,861 per QALY gained for patients with only one prior therapy and £22,589 per QALY gained for patients who had received two or more prior therapies.

3.15 The ERG explored the precision with which the fitted curve for len/dex matched the actual trial data used in the model. It observed that the fitted curve overestimated overall survival. The ERG noted that the overall survival curve for the dexamethasone arm in the cost-effectiveness model had been adjusted to predict the median overall survival predicted from the MRC trials. However, the ERG stated that it was more methodologically correct to adjust the dexamethasone overall survival calculation in the model to predict the mean overall survival predicted from the MRC trials, because

the ICERs calculated from the model were a ratio of means and not medians.

3.16 The ERG conducted an exploratory analysis with an improved fit of the len/dex overall survival curve and also with the dexamethasone curve adjusted to the mean overall survival in the MRC trials. For the subgroup of patients who had received only one prior therapy where len/dex was compared with bortezomib, the ICER increased more than 30-fold from the manufacturer's base case. For the subgroup who had received one prior therapy where the comparator was dexamethasone, the ICER increased from £46,865 to £69,500 per QALY gained. For the subgroup of patients who had received two or more prior therapies, the ICER increased from £24,584 to £47,100 per QALY gained. For patients who had received prior thalidomide, the ICER increased from £38,861 to £56,500 per QALY gained if they had received only one prior therapy and from £22,589 to £43,600 per QALY gained if they had received two or more prior therapies.

3.17 In addition, the ERG noted that the costs associated with routine medical management (non-drug costs) assumed in the model were lower than the figures that were accepted in the appraisal of bortezomib and may therefore have been underestimated. It also noted that the model had no disutility attached to the occurrence of adverse effects. Finally, it noted that the cost of anti-thrombotic prophylaxis that was routinely used with lenalidomide was not included in the model. The ERG stated that the inclusion of the above considerations in the model would further increase the ICERs for all subgroups above the values obtained in the exploratory reanalyses quoted above.

3.18 For the subgroup of patients who had received only one prior therapy, the ERG repeated the indirect comparison of len/dex with bortezomib using methods that it considered to be more

appropriate. This resulted in a hazard ratio of 0.557 (95% CI 0.337 to 0.912). The ERG pointed out that this comparison was with bortezomib as monotherapy and that bortezomib was commonly used in combination with dexamethasone in routine clinical practice. The economic analysis for the comparison of len/dex with bortezomib also assumed a maximum of eight cycles of bortezomib instead of the 11 allowed in the trial, and did not model the response-based rebate scheme recommended in NICE technology appraisal guidance 129. The ERG also suggested that the administration costs associated with bortezomib may have been overestimated in the manufacturer's model. In addition, the dose intensity for bortezomib was assumed to be 100%; that is, the analysis did not allow for dose reductions and treatment interruptions, which had been included for lenalidomide. All of the above issues would have had the effect of increasing the ICERs for the comparison of len/dex with bortezomib in the subgroup of patients who had received only one prior therapy.

3.19 After the first Appraisal Committee meeting, the manufacturer presented an updated cost-effectiveness analysis. The manufacturer stated that this updated analysis would only consider all patients who had received two or more prior therapies and the subgroup of patients who had received thalidomide as one of these prior therapies. The manufacturer accepted the ERG's approach to modelling the len/dex overall survival curve. However, the manufacturer did not agree with the calibration of the overall survival curve for dexamethasone alone in the cost-effectiveness model to the mean overall survival predicted from the MRC trials. The manufacturer stated that a curve calibrated to the mean rather than the median overall survival was less representative of the published curves, and that using the mean placed more emphasis on the tail of the distribution, where there were fewer patients and greater uncertainty. The manufacturer maintained that it was

appropriate to calibrate the curve to the predicted median survival in the updated analysis. In addition, the updated analysis incorporated costs for outpatient visits into routine management costs, and inflated the routine management costs to 2008 values. The effects of adding costs for the prophylaxis of deep vein thrombosis and disutility for long-term adverse effects were also explored in the updated model through sensitivity analyses. The manufacturer also proposed a patient access scheme in which the cost of lenalidomide to the NHS for a person with multiple myeloma will be capped at 26 cycles of treatment (each of 28 days, so normally administered over 2 years). A cycle will still be considered as having been completed within the scheme even if there are dose reductions and treatment interruptions during the cycle. The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles will be met by the manufacturer. The Department of Health in England and the Department of Health and Social Services in Wales accepted the consideration of this scheme by NICE.

3.20 Taking all these factors into account in the model, for patients who had received two or more prior therapies the incremental life-year gain was 2.77, the incremental QALY gain was 1.86 and the ICER was £30,350 per QALY gained. For patients who had received thalidomide as one of the prior therapies the incremental life-year gain was 2.51, the incremental QALY gain was 1.7 and the ICER was £28,941 per QALY gained. These ICERs were relatively insensitive to the addition of costs for prophylaxis of deep vein thrombosis or disutility for long-term adverse effects.

3.21 The ERG considered the updated analyses from the manufacturer and agreed with the implementation of the stated changes. It noted that the model predicted that, for the group of patients who had received two or more prior therapies, the patient access scheme applied to 17% of the people in the model. The estimated average

cost of treatment to the NHS per person with lenalidomide over a modelled lifetime (median overall survival approximately 2.7 years) decreased from £59,800 to £51,800 with the patient access scheme. For the subgroup of patients who had received thalidomide as one of their prior therapies the patient access scheme applied to 11% of people in the model, and the modelled lifetime cost of treatment to the NHS per person with lenalidomide decreased from £49,800 to £46,300 with the patient access scheme.

3.22 The ERG repeated the exploratory analysis on the updated model using their preferred approach with the dexamethasone overall survival curve calibrated to the mean survival predicted from the MRC trials and the patient access scheme implemented in the model. For the subgroup of patients who had received two or more prior therapies, the incremental life-year gain was 1.81 and the incremental QALY gain was 1.24 at an incremental cost of £54,291, giving an ICER of £43,800 per QALY gained. For patients who had received thalidomide as one of the prior therapies, the incremental life-year gain was 1.71 and the incremental QALY gain was 1.15 at an incremental cost of £47,531, giving an ICER of £41,300 per QALY gained.

3.23 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lenalidomide, having considered evidence on the nature of the condition and the value placed on the benefits of lenalidomide by people with multiple myeloma, those

who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee understood that multiple myeloma is an incurable disease. It was aware that the disease and its course are heterogeneous and that for relapsed multiple myeloma the choice of therapy for a particular person is influenced by the initial treatment and their response to it, the inherent characteristics of the disease and the person's performance status and preferences. The Committee heard from clinical specialists and patient experts that lenalidomide is an important advance in the treatment of multiple myeloma and could be considered as an alternative to bortezomib (currently recommended as a treatment option in NICE technology appraisal guidance 129) at first relapse. The Committee noted the importance that patients, their carers and physicians placed on having effective options to treat multiple myeloma at presentation and at subsequent relapses. However, it understood that the optimal sequence of agents to use is as yet unclear and depends on several factors, including a person's treatment history, comorbidities and disease characteristics.

4.3 The Committee understood that, in accordance with current NICE guidance (NICE technology appraisal guidance 129), bortezomib is routinely used in clinical practice for the treatment of progressive multiple myeloma in people who are at first relapse having received only one prior therapy. Therefore it considered bortezomib to be the most appropriate comparator for lenalidomide in people who have had only one prior therapy. The Committee noted that bortezomib is usually used in combination with dexamethasone, but that there is variation in clinical practice and limited formal evidence for the superior efficacy of this combination compared with bortezomib monotherapy.

4.4 The Committee considered the options available for the treatment of multiple myeloma at second and subsequent relapse. Current NICE guidance restricts the use of bortezomib to first relapse because the use of bortezomib at subsequent relapses was found not to be cost effective (NICE technology appraisal guidance 129), with ICERs of £77,000 or more per life year gained. Thalidomide is not licensed for this indication, and an application for a licence for the treatment of relapsed or refractory multiple myeloma was withdrawn. However, thalidomide is used as a treatment option for multiple myeloma within the NHS, although the extent of this use is not known. The Committee also noted a statement from the manufacturer that there is a lack of evidence for the efficacy of thalidomide for this indication, particularly after failure of two or more therapies. The Committee understood that a variety of other regimens could be used at second and subsequent relapse, but that no studies had been identified that have demonstrated the superiority of these compared with dexamethasone alone. Therefore it accepted that in people who have received two or more prior therapies, high-dose dexamethasone was a reasonable comparator for lenalidomide.

4.5 The Committee discussed the RCTs comparing len/dex with dexamethasone alone for the management of relapsed multiple myeloma. It noted that TTP (the primary outcome) was statistically significantly increased in the len/dex arm for the whole trial population as well as in subgroups of people who had received prior therapy with bortezomib or thalidomide. It considered that the RCTs provided evidence that overall survival and response rates were also higher with len/dex compared with dexamethasone alone. The Committee concluded that the len/dex combination improved outcomes in people with relapsed multiple myeloma when compared with dexamethasone. This included people who

had received either one or two or more prior therapies, and when prior therapies included the use of thalidomide.

4.6 The Committee next discussed the relative effectiveness of len/dex compared with bortezomib. It noted that the evidence for the effectiveness of len/dex compared with bortezomib monotherapy was derived from an indirect comparison via the common comparator of high-dose dexamethasone. It considered that there was uncertainty in the results of the indirect comparison because of heterogeneity between the studies, such as differences in the regimen of dexamethasone and the definition of response. The Committee noted that there was additional uncertainty in interpreting the context of current practice, as it understood that bortezomib is usually used in combination with dexamethasone in clinical practice.

4.7 The Committee discussed the adverse effects associated with lenalidomide. It noted that from the patients' viewpoint lenalidomide is associated with a more favourable adverse effect profile than most other regimens and agents used in the management of relapsed multiple myeloma. It heard from clinical specialists and patient experts that lenalidomide might be particularly useful for people with pre-existing peripheral neuropathy in whom the use of bortezomib at first relapse is restricted. However, the Committee noted that lenalidomide is associated with a statistically significant increased risk of venous thrombosis and embolism. It heard from clinical specialists that this risk is usually managed with prophylaxis in the form of low-dose aspirin in people with multiple myeloma. However, in people with a history of venous thromboembolism or other relevant risk factors, the use of warfarin or low-molecular-weight heparin would be considered. The Committee heard that with such prophylaxis the risk would return to baseline levels. The additional cost incurred for the management of people with multiple myeloma would be minimal if low-dose aspirin was used, but could

have an impact if either low-molecular-weight heparin or warfarin was needed.

4.8 The Committee considered the manufacturer's economic evaluation of the use of lenalidomide and the critique from the ERG. It accepted that the general structure of the manufacturer's model was reasonable. It considered that the subgroups in the model were those relevant to decision-making in routine clinical practice. It discussed the sensitivity and scenario analyses presented by the manufacturer, as well as those explored by the ERG using the manufacturer's model. In particular, the Committee discussed the methods used for adjustment for the crossover effect in the RCTs, the extrapolation of survival data, the costs of medical management and administration of bortezomib therapy, and the utility values reflecting health-related quality of life for the pre-progression and post-progression states and from adverse effects.

4.9 The Committee noted that the trial results included a crossover effect and considered whether it was appropriate to use data from historical MRC trials to predict survival for people treated with dexamethasone in this population in the absence of an unbiased estimate from the trials of lenalidomide. The Committee was aware that the MRC data were derived from trials of agents in first-line therapy for multiple myeloma. Despite this, it accepted that these data represented the best available survival data for people with multiple myeloma to be used in extrapolation of overall survival in the current analysis. The Committee also noted that use of these data assumed that dexamethasone monotherapy was a suitable proxy (in the absence of more specific evidence) for all anti-myeloma therapies used in relapse. The Committee also considered that there was no evidence to indicate that the effectiveness of dexamethasone in relation to survival had changed over time since the MRC trials. It accepted the statements from the clinical specialists indicating that where improvements were noticed

these were likely to be attributable to the use of the newer agents and stem-cell transplantation.

4.10 The Committee considered the ERG's exploratory reanalysis with an improved fit of the len/dex overall survival curve to the trial data and calibration of the dexamethasone overall survival curve to predict mean (and not median) overall survival based on a risk equation for survival derived from the MRC trials. The Committee considered that the ERG's approach to modelling overall survival in both the len/dex and dexamethasone arms was valid and resulted in more plausible estimates of cost effectiveness than those presented by the manufacturer. The Committee noted that these adjustments to the modelling of survival may have different effects in different subgroups and that the ERG's adjustments had been made separately to subgroups defined according to number of prior therapies.

4.11 The Committee considered the base-case ICERs resulting from the manufacturer's economic analysis, as well as the results of the ERG's exploratory analysis using the alternative approach to the modelling of overall survival. It noted that, in the manufacturer's base case, none of the ICERs for lenalidomide for the subgroups with only one prior therapy were within the range that would normally be considered a cost-effective use of NHS resources. The Committee noted that the comparison of len/dex with bortezomib in the subgroup of people who had received only one prior therapy resulted in a high ICER. The Committee also considered that the ICER for the comparison with bortezomib would increase further if the model took into account: the bortezomib response-based rebate scheme (as described in NICE technology appraisal guidance 129); the lower costs of bortezomib administration suggested by the ERG; the higher maximum number of cycles of bortezomib; and the likely dosage reduction for bortezomib. When the ERG's approach to modelling overall survival was used, the

ICER was more than £69,000 per QALY gained for the comparison of lenalidomide with dexamethasone in people who had received one prior therapy only. For the comparison with dexamethasone in people who had received one prior therapy and that therapy was thalidomide, the ICER was more than £56,000 per QALY gained.

4.12 The Committee considered other issues with the base-case analysis. The model did not fully include costs and utility decrements owing to adverse effects, and the Committee considered that if appropriate costs and disutilities for adverse effects and anti-thrombosis prophylaxis were used in the model, the ICERs for lenalidomide would increase. It also noted that the utility in the model for the pre-progression state was that of the normal population at age 54 years, and that this is considerably younger than the average age of people who usually develop multiple myeloma. The Committee noted the results of the exploratory analysis by the ERG, which showed that using lower administration costs for bortezomib, using higher costs for routine medical management and modelling the bortezomib response-based rebate scheme all had the effect of increasing the ICERs for lenalidomide for the subgroup of patients who had received one prior therapy. The Committee concluded that, in the light of these additional issues, the most plausible ICERs in all subgroups would be higher than those stated in 4.11.

4.13 The Committee discussed the updated analysis presented by the manufacturer. It noted that the manufacturer had chosen not to present any new analysis for people who had received only one prior therapy. The Committee discussed whether there were any further factors that would have a bearing on its considerations about the cost effectiveness of lenalidomide in this patient group. These included the degree of certainty in the ICERs, the severity of the illness experienced by people with multiple myeloma who have received one prior therapy and the innovative nature of

lenalidomide. It did not identify any factors that would alter its conclusions based on the evidence currently available. Overall, the Committee concluded that the use of lenalidomide for the treatment of multiple myeloma in people who had received only one prior therapy would not be a cost-effective use of NHS resources.

4.14 The Committee considered the subgroups of people who had received two or more prior therapies, including the subgroup who had received thalidomide as one of these therapies. When the ERG's approach to modelling overall survival was used, the ICERs for lenalidomide for these subgroups increased to at least £47,100 per QALY gained for those who had received two or more prior therapies, and to at least £43,600 per QALY gained for those who had received two or more prior therapies of which one was thalidomide.

4.15 The Committee discussed the updated analysis from the manufacturer and the exploratory reanalysis by the ERG for people who had received two or more prior therapies. The Committee concluded that the changes to the len/dex curve, utilities and costs had been implemented appropriately. The Committee noted that the variable that had the greatest impact on cost effectiveness was the method of calibrating the dexamethasone overall survival curve in the economic model (that is, to the predicted median or mean survival for the trial population) from the risk equation for survival derived from the MRC trials. The Committee noted that the data from the MRC trials were complete, with most participants having reached the outcome of interest (that is, there was very little censoring of the data), and that in such a situation the mean was a better estimate of average survival. It considered that, since the mean overall survival was used in the calculations of cost effectiveness, calibrating the overall survival predicted by the MRC data calibration model to the mean was more representative of the costs and benefits for this population. In addition, the Committee

noted that when median survival was used to calibrate the survival curve, the improvement in overall survival predicted by the model was out of proportion to the observed improvement in progression-free survival from the lenalidomide trials. This relationship between the progression-free survival and overall survival from the lenalidomide trials was, however, maintained when calibrating the overall survival curve in the dexamethasone arm to the mean survival predicted from the MRC trials. The Committee understood that the choice between the use of mean or median survival was a scientific judgement, but concluded that for the purposes of decision making in this situation, the ICER estimates from using the mean were most appropriate.

4.16 The Committee accepted that the patient access scheme for lenalidomide was correctly implemented by the manufacturer in the economic evaluation. It noted that, in the economic model, the patient access scheme was included by capping the maximum cost of lenalidomide for an individual patient at 26 cycles of 28 days each, equivalent to 2 years. The Committee noted that the manufacturer stated that treatment interruptions within cycles were generally short, and that no patients missed entire cycles in the clinical trial. The cost of lenalidomide per cycle in the model was adjusted, as in the base case, to take into account the treatment reductions and interruptions noted in the first 23 cycles in the trials. The Committee concluded that the relevant and appropriate ICERs upon which to make a decision were £43,800 per QALY gained for the subgroup of patients who had received two or more prior therapies and £41,300 per QALY gained for the subgroup who had received two or more prior therapies including thalidomide. These ICERs represented the cost effectiveness of lenalidomide with the patient access scheme triggered after 26 cycles, regardless of any dose reductions or treatment interruptions that may occur during a cycle, and were the basis for the Committee's decisions.

4.17 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.18 The Committee next discussed whether the subgroup of people with multiple myeloma who had received two or more prior therapies, and the benefit provided by lenalidomide, fulfilled the criteria for consideration as an appraisal of a life-extending, end-of-life treatment. The Committee noted from the clinical trials and the MRC data that normal life expectancy without lenalidomide was unlikely to be greater than 24 months and was potentially as low as 9 months. The Committee considered that evidence from the lenalidomide trials suggested that lenalidomide increased survival by more than 3 months compared with dexamethasone, and that crossover in the dexamethasone arm means that this benefit is likely to have been underestimated. The Committee considered

that the potential alternatives, thalidomide and bortezomib, were unlikely to be routinely available on the NHS, as discussed in section 4.4. The Committee noted from the manufacturer's submission that the estimated eligible population was approximately 2100. In summary, the Committee was satisfied that the population and the technology of interest meet the criteria for accepting that this is an appraisal of a life-extending, end-of-life treatment and that the evidence presented for this consideration was supported by robust data.

4.19 The Committee subsequently considered the ERG's cost-effectiveness estimates using the manufacturer's model in the context of a life-extending, end-of-life treatment. It noted that the QALY increment associated with the most plausible cost-effectiveness estimates was approximately 1.24 QALYs. The Committee considered that the magnitude of the additional weight that would need to be assigned to the original QALY benefit for the cost effectiveness of lenalidomide to fall within the currently applied ICER threshold range was acceptable. Additionally, the Committee noted from the model that the extension to life with lenalidomide was approximately 1.81 years. The Committee considered that the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age, was acceptable.

4.20 In summary, the Committee accepted that, for people with multiple myeloma who had received two or more prior therapies, the most plausible ICERs were those suggested by the ERG on the basis of exploration of the manufacturer's model and with the implementation of the patient access scheme (where the manufacturer would bear the costs of lenalidomide beyond 26 cycles [normally 2 years] for people whose disease had not progressed at this time). For the purpose of the recommendations,

the patient access scheme would be triggered by the completion of 26 cycles (which normally takes 2 years), regardless of treatment interruptions and dose reductions within those cycles. The Committee accepted that the benefits provided by lenalidomide fitted the criteria for consideration for appraising a life-extending, end-of-life treatment. The Committee concluded that the additional weights that need to be attached to the QALYs to achieve ICERs within the normal threshold range are acceptable in these circumstances. Consequently the Committee recommended lenalidomide, within its licensed indication, as an option for the treatment of multiple myeloma in people who have received two or more prior therapies. The Committee noted that some people who have not received two or more prior therapies may be currently receiving lenalidomide for the treatment of multiple myeloma, and recommended that these people should have the option to continue treatment until they and their clinician consider it appropriate to stop.

5 Implementation

5.1 The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website.

5.2 The Welsh Assembly Minister for Health and Social Services issued a direction in October 2003 that requires local health boards and NHS trusts to make funding available to implement NICE technology appraisal guidance, normally within 3 months of the guidance being published.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee considered that rigorous data collection is needed on the life-extending benefits of lenalidomide when used in people with multiple myeloma who have received two or more prior therapies.

7 Related NICE guidance

Published

- Bortezomib monotherapy for relapsed multiple myeloma. NICE technology appraisal guidance 129 (2007). Available from www.nice.org.uk/TA129
- Guidance on cancer services – improving outcomes in haematological cancers (2003). Available from www.nice.org.uk/CSGHO

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by NICE, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in October 2010 together with the guidance on bortezomib (NICE technology appraisal guidance 129).

David Barnett
Chair, Appraisal Committee
April 2009

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey

Lay member

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queen's University, Belfast

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology

Dr Neil Milner

General Practitioner, Tramways Medical Centre, Sheffield

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay member

Professor Ken Stein

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Ms Nathalie Verin

Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts

Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

Mr Tom Wilson

Director of Contracts and Information Management and Technology, Milton Keynes Primary Care Trust

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Elangovan Gajraj

Technical Lead

Helen Chung, Prashanth Kandaswamy

Technical Advisers

Shaun Minehan, Jeremy Powell

Project Managers

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG):

- 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 The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Celgene

II Professional/specialist and patient/carer groups:

- Leukaemia CARE
- Leukaemia Research Fund
- Macmillan Cancer Support
- Myeloma UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal College of Radiologists
- UK Myeloma Forum

III Other consultees

- Department of Health
- Rotherham Primary Care Trust

- Sandwell Primary Care Trust
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal)

- Celgene/Pharmion
- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline
- Janssen-Cilag
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group
- Pfizer
- Schering-Plough

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on lenalidomide by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Michael Brown, nominated by Myeloma UK – patient expert
- Dr Jamie Cavenagh, Consultant Haematologist, Barts and the London NHS Trust, nominated by the UK Myeloma Forum – clinical specialist
- Mr Eric Low, Chief Executive, Myeloma UK, nominated by Myeloma UK – patient expert
- Dr Steve Schey, Consultant Haematologist, Kings College Hospital, nominated by National Cancer Research Institute (NCRI)/Royal College of Physicians (RCP)/Royal College of Radiologists(RCR)/Association of Cancer Physicians (ACP)/ Joint Collegiate Council on Oncology (JCCO) – clinical specialist