

Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib

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Contents

1 Guidance	3
2 The technology	4
3 The company's submission	5
Clinical effectiveness.....	5
Cost effectiveness	9
ERG comments on the clinical effectiveness	14
ERG comments on the cost effectiveness	16
Company's additional evidence.....	20
4 Consideration of the evidence	24
Clinical effectiveness.....	26
Cost effectiveness	31
Summary of Appraisal Committee's key conclusions.....	40
5 Implementation	46
6 Review of guidance	47
7 Appraisal Committee members, guideline representatives and NICE project team.....	48
Appraisal Committee members	48
NICE project team	50
8 Sources of evidence considered by the Committee	51
About this guidance	53

1 Guidance

- 1.1 Pomalidomide, in combination with dexamethasone, is not recommended within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.

- 1.2 People whose treatment with pomalidomide was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Pomalidomide (Imnovid, Celgene) is an oral immunomodulatory drug analogue of thalidomide that directly inhibits myeloma growth. Pomalidomide in combination with dexamethasone has a UK marketing authorisation for the 'treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy'.
- 2.2 The summary of product characteristics lists the following 'very common' adverse reactions for pomalidomide: anaemia, bone pain, constipation, cough, decreased appetite, diarrhoea, dyspnoea, fatigue, leucopenia, muscle spasms, nausea, neutropenia, peripheral oedema, pneumonia, pyrexia and thrombocytopenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Pomalidomide is administered orally. The recommended dosage is 4 mg once daily, taken on days 1 to 21 of repeated 28-day cycles. Treatment should continue until disease progression. Adverse reactions may be managed by interrupting or reducing the dose, as specified in section 4.2 of pomalidomide's summary of product characteristics. The price of a pack (21 tablets) of 1 mg, 2 mg, 3 mg or 4 mg tablets is £8884 (excluding VAT; British National Formulary [BNF] edition 67). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee ([section 7](#)) considered evidence submitted by the manufacturer of pomalidomide and a review of this submission by the Evidence Review Group (ERG; [section 8](#)).

Clinical effectiveness

- 3.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of pomalidomide plus low-dose dexamethasone for treating multiple myeloma in people who previously had lenalidomide and bortezomib. It identified 1 phase III randomised controlled trial, MM-003.
- 3.2 The MM-003 study was an international, multicentre (93 centres in Europe, Russia, Australia, Canada and USA), open-label phase III trial in 455 adults with relapsed and refractory multiple myeloma which had been treated with at least 2 treatment regimens, including both lenalidomide and bortezomib. Randomisation was stratified by age, disease population (that is, patients whose disease was refractory; relapsed and refractory; and refractory or intolerant), and number of previous multiple myeloma treatments. Patients were then randomised 2:1 to pomalidomide 4 mg daily plus low-dose dexamethasone 40 mg on days 1, 8, 15 and 22 of a 28-day cycle (n=302; hereafter referred to as pomalidomide), or high-dose dexamethasone 40 mg on days 1 to 4, 9 to 12 and 17 to 20 of a 28-day cycle (n=153; hereafter referred to as dexamethasone). In both treatment groups, the dexamethasone dose was reduced to 20 mg in patients aged 75 years or more. Treatment continued until disease progressed or there was unacceptable toxicity. After treatment stopped, patients were assessed at 28 days and had 4 follow-up visits per year until either death or 5 years after randomisation.
- 3.3 The company stated that the baseline characteristics of the patients enrolled in the MM-003 study were well balanced between the 2 treatment groups. Over 80% of patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Median ages were 64 years in patients randomised to pomalidomide and 65 years in patients randomised to dexamethasone. Patients in both groups had a median of 5 previous treatments, and the

median time from diagnosis was 5.3 years in the pomalidomide group and 6.1 years in the dexamethasone group. Approximately one third of patients in both treatment groups had stage III disease based on the International Staging System for multiple myeloma (31% versus 35%). Approximately three quarters of patients in both groups had disease that was refractory to both lenalidomide and bortezomib (75% versus 74%), and a similar proportion of patients had previous stem cell transplantation (71% versus 69%). The company noted that the population in the MM-003 study may not be generalisable to the population specified in the marketing authorisation, because patients in the study had more previous treatments and more refractory disease. The company also highlighted that the median age of patients in clinical practice in England is likely to be higher than that in the MM-003 study.

- 3.4 The primary outcome measure in MM-003 was progression-free survival assessed by an Independent Response Adjudication Committee. An intention-to-treat population was used to analyse the efficacy outcomes after a median follow-up of 10 months. Median progression-free survival was 16.0 weeks with pomalidomide and 8.1 weeks with dexamethasone (hazard ratio [HR] 0.49, 95% confidence interval [CI] 0.39 to 0.61). The company presented the results from subgroup analyses for 18 pre-specified subgroups and the 3 stratification factors. Each analysis favoured pomalidomide over dexamethasone and most reached statistical significance at the 5% level. A sensitivity analysis using time-to-treatment failure (defined as the earliest of disease progression, stopping treatment, death or starting another myeloma therapy) was presented. Median time-to-treatment failure was 12.4 weeks with pomalidomide and 8.0 weeks with dexamethasone (HR 0.48, 95% CI 0.39 to 0.60).
- 3.5 Secondary outcomes reported in the MM-003 study included overall survival, response rates and assessment of health-related quality of life. Median overall survival was longer with pomalidomide than with dexamethasone in the intention-to-treat population (54.0 versus 34.9 weeks; HR 0.70, 95% CI 0.54 to 0.92). In this analysis, 48.7% of patients (n=146) in the pomalidomide group died compared with 56.0% of patients (n=84) in the dexamethasone group. In the analyses in which the company used statistical methods to adjust the survival estimates for treatment switching, median overall survival was

12.7 months with pomalidomide and 5.7 or 6.7 months with dexamethasone using the two-stage Weibull method (HR 0.52, 95% CI 0.39 to 0.68) or RPSFTM method (HR 0.49, 95% CI 0.33 to 1.00), respectively.

- 3.6 Objective response rates (defined as complete or partial response) were 23.5% with pomalidomide and 3.9% with dexamethasone. Partial response was observed in 20.5% and 3.3% of patients randomised to pomalidomide and dexamethasone respectively.
- 3.7 Health-related quality of life was measured on day 1 of each treatment cycle and again when treatment stopped using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire for patients with cancer (QLQ-C30), the EORTC multiple myeloma module (QLQ-MY20) and the EuroQol-5 dimensions survey (EQ-5D). Most results presented by the company suggest favourable trends with pomalidomide compared with dexamethasone.
- 3.8 The company reported that the proportions of patients who experienced at least 1 adverse reaction were similar between those taking pomalidomide (n=297, 99.0%) and those taking dexamethasone (n=149, 99.3%). The company reported grade 3 or 4 adverse reactions in 259 out of 300 patients taking pomalidomide (86.3%) and 127 out of 150 patients taking dexamethasone (84.7%). The most common grade 3 or 4 adverse reactions reported for pomalidomide compared with dexamethasone were anaemia (32.7% versus 38.7%), leucopenia (9.0% versus 3.3%), neutropenia (48.3% versus 15.3%), pneumonia (12.7% versus 8.0%) and thrombocytopenia (22.0% versus 26.0%). Stopping treatment because of an adverse reaction was observed in 8.6% and 10.5% of patients taking pomalidomide and dexamethasone respectively. Dose interruptions (67.0%) were more common than dose reductions (27.3%) in patients taking pomalidomide. The company also reported serious adverse reactions in 183 of 300 patients (61.0%) taking pomalidomide and 80 of 150 patients (53.3%) taking dexamethasone. A total of 11 (3.7%) treatment-related deaths were reported in the pomalidomide group and 7 (4.7%) in the dexamethasone group.

- 3.9 For the comparators, the company's systematic literature review identified 2 observational studies (Gooding et al. 2013 poster presentation, n=30; Tarant et al. 2013 abstract, n=55). Both of these unpublished, retrospective studies were done in single centres in England, and reported results from patients whose disease had several treatments including, but not limited to, bendamustine, re-treatment with bortezomib, re-treatment with lenalidomide and re-treatment with thalidomide.
- 3.10 Gooding et al. (2013) described the efficacy of fourth-line therapy in 30 patients with relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. The median age of patients was 65.3 years, median time from diagnosis was 11.5 years, and patients had a median of 3 previous treatments. International Staging System for multiple myeloma scores at diagnosis were: 17% stage I, 27% stage II and 33% stage III (23% unclassified). Median progression-free survival was 11 weeks and median overall survival was 23 weeks. The most common fourth-line treatment contained bendamustine (53%) and no patients had high-dose dexamethasone. Patients were treated for a mean of 15.3 weeks. Complete response, very good partial response and partial response were seen in 3.3%, 6.7% and 16.5% of patients respectively. The most commonly reported grade 3 or 4 adverse reactions were anaemia (60%), bone pain (37%) and thrombocytopenia (43%).
- 3.11 Tarant et al. (2013) assessed the survival of 55 patients with relapsed multiple myeloma after sequential thalidomide-, bortezomib- and lenalidomide-based combination therapies. Of the 55 patients, 26 had fourth-line therapy. Median age was 59 years, median time from diagnosis was 4.4 years and patients had a median of 3 previous treatments. International Staging System for multiple myeloma scores at diagnosis were: 20% stage I, 28% stage II and 28% stage III (23% unclassified). Median progression-free survival was not reported and median overall survival was 3.9 months. Response rates and adverse reactions were not reported.
- 3.12 The company did not conduct a mixed treatment comparison to compare the effectiveness of pomalidomide with that of the comparators listed in the scope of the appraisal. It stated that this was because the evidence for comparator

technologies came from studies including single treatment groups, and therefore the company could not identify a common comparator that would allow it to create a network.

Cost effectiveness

3.13 The company did not identify any published cost-effectiveness studies of pomalidomide plus low-dose dexamethasone for treating relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. It therefore developed a semi-Markov partitioned survival model with a cycle length of 1 week to account for rapid progression and mortality observed in the population with relapsed and refractory multiple myeloma. The model included a half-cycle correction and 4 health states: progression-free disease, split into 'on treatment' and 'off treatment'; progressed disease; and death. The model assumed that a patient could be offered 1 of 4 treatments:

- pomalidomide plus low-dose dexamethasone
- bortezomib plus high-dose dexamethasone
- thalidomide plus high-dose dexamethasone and cyclophosphamide
- bendamustine plus thalidomide and low-dose dexamethasone.

The primary outcome of the model was quality-adjusted life years (QALYs). Costs from an NHS perspective and health effects (in terms of QALYs) were discounted over a patient's lifetime time horizon (25 years) at an annual rate of 3.5%.

3.14 The proportion of patients in each health state was calculated using the time-to-treatment failure, progression-free survival and overall survival data from the MM-003 study and Gooding et al. (2013). The company considered the Gooding et al. study the most appropriate data source because it was the only source that presented patient-level data. The company also considered the populations in MM-003 and Gooding et al. to be comparable, and that the 3 comparator regimens (see section 3.13) had the same efficacy. According to the company, this was supported by its post hoc analysis of 66 patients from the MM-003 study that showed no statistically significant differences between post-progression survival and the 7 different treatments given after disease

progression ($p=0.7806$). The company stated that clinical expert opinion also supported the assumption of equal efficacy. The company noted that it found no significant differences between bendamustine and any of the other treatments for overall survival ($p=0.38$), progression-free survival ($p=0.38$) and time-to-treatment failure ($p=0.74$) in the Gooding et al. study, providing further support for its assumption of equal efficacy.

- 3.15 To extrapolate outcomes beyond the timeframe of the studies, the company fitted a series of parametric curves to the MM-003 and Gooding et al. (2013) data using exponential, extreme value, log-logistic, log-normal and Weibull distributions. The company stated that it selected the most appropriate parametric function for each clinical outcome using statistical tests and visual inspection to assess goodness of fit, as well as incorporating advice from UK clinicians about how well the curves reflect long-term survival. In the base-case analysis the company used the extreme value function for time-to-treatment failure, and log-logistic function for progression-free survival and for overall survival.
- 3.16 The company stated that it used the list prices for bortezomib and bendamustine because there is no publicly available information on any price reductions in the Cancer Drugs Fund for these drugs. The company stated that treatment was interrupted in some patients taking pomalidomide in the MM-003 study because of adverse reactions and this was accounted for in its economic model. The company assumed that 17% of patients taking pomalidomide had a treatment interruption in the first cycle, and that this proportion decreased with each subsequent cycle. To model dosages for the comparator technologies, the company used the dosing regimens from the summary of product characteristics; for thalidomide plus dexamethasone and cyclophosphamide, it used data from Gooding et al. (2013). However, it did not restrict the number of cycles of bortezomib to a maximum of 8 as stipulated in the drug's summary of product characteristics because it considered that this did not accurately reflect clinical practice. It stated that the economic model accounted for drug wastage across all treatments. For the treatments administered intravenously or subcutaneously, the model included an outpatient visit for each administration. Costs associated with managing 'progression-free disease' included routine monitoring, blood transfusions,

concomitant medications and adverse reactions to treatment. Costs associated with managing 'progressed disease' included routine monitoring, blood transfusions and a one-off cost for terminal care (£854) incurred at death. In the base-case analysis, the company did not include costs relating to subsequent therapies because it was uncertain about what treatments were used beyond fourth line.

- 3.17 To estimate health-related quality of life, the company undertook a multivariate regression analysis using EQ-5D data from the MM-003 study. The company's multivariate regression analysis estimated utility values of 0.75, 0.65 and 0.61 for responsive disease, stable disease and progressed disease respectively. For the 'progression-free' health state, it used the best overall response rates from the MM-003 study and Gooding et al. (2013) to estimate a utility value for pomalidomide and the comparators. The company's multivariate regression analysis also estimated disutility values of 0.037 for the transition to the progressed disease health state and 0.138 for hospitalisation. The company also included a disutility value of 0.025 per cycle for people taking intravenous or subcutaneous therapies, taken from NICE technology appraisal guidance on [erlotinib for the treatment of non-small-cell lung cancer](#).
- 3.18 The company included costs and disutility values associated with adverse reactions in its base-case analysis. Those included in the company's economic model related to grade 3 or 4 adverse reactions seen in 2% or more patients taking pomalidomide in the MM-003 study. The company assumed that the cost of each adverse reaction depends on whether the reaction is actively treated and the setting in which care is provided.
- 3.19 The company's economic model estimated median overall survival of 0.977 years for pomalidomide and 0.422 years for the comparators (the actual median overall survival data from the MM-003 study and Gooding et al. were 1.035 years for pomalidomide and 0.441 years for the comparators). The company's economic model estimated a median progression-free survival of 0.307 years for pomalidomide and 0.249 years for the comparators (the actual median progression-free survival data were 0.307 years for pomalidomide and 0.219 years for the comparators). The company stated that in multiple myeloma, Felix et al. (2013) found an average increase of 2.45 months (95%

CI 1.7 to 3.2) in median overall survival for each additional month reported for median time-dependent end points (such as progression-free survival). The company stated that this was consistent with the outcomes of the MM-003 study.

- 3.20 The company's economic model estimated total mean life years gained of 2.225 for pomalidomide and 1.166 for the comparators (that is, 1.059 additional life years [12.7 months] with pomalidomide compared with the comparators). Of the total life years gained, 1.596 and 0.579 life years were gained in the progressed disease health state for pomalidomide and the comparators respectively; that is, most of the benefit, 1.018 incremental life years, was gained in the progressed disease health state.
- 3.21 The company presented deterministic incremental cost-effectiveness ratios (ICERs) for pomalidomide compared with each of the comparators included in its economic model. The company stated that a fully incremental analysis was not appropriate because of its assumption of equal efficacy for the comparators, and also because the differences in QALYs lost due to adverse reactions and administration were negligible between treatments. For pomalidomide compared with:
- bortezomib plus dexamethasone, the company estimated incremental costs of £30,782 and 0.61 incremental QALYs gained, with an ICER of £50,366 per QALY gained
 - thalidomide plus dexamethasone and cyclophosphamide, the company estimated incremental costs of £47,219 and 0.61 incremental QALYs gained, with an ICER of £77,915 per QALY gained
 - bendamustine plus thalidomide and dexamethasone, the company estimated incremental costs of £44,142 and 0.61 incremental QALYs gained, with an ICER of £72,250 per QALY gained.
- 3.22 The company presented the results of a univariate sensitivity analysis and several scenario analyses. The univariate sensitivity analysis suggested that the ICERs for pomalidomide were most sensitive to parameter estimates for the overall survival curves, particularly those for the comparator technologies

from Gooding et al. (2013). The company commented that this was likely to be caused by the small population included in the Gooding et al. study. The company stated that the scenario analyses suggested that the ICER was relatively insensitive to structural changes across all comparisons. However, its scenario analyses showed that the ICERs were most sensitive to the time horizon of the economic model, to whether or not patients stopped treatment at disease progression (rather than based on time-to-treatment failure data), and to alternative parametric distributions selected for overall survival, progression-free survival and time-to-treatment failure:

- ICERs for pomalidomide compared with bortezomib plus dexamethasone ranged from £42,440 (log-normal function to model overall survival) to £92,521 (Weibull function to model overall survival) per QALY gained.
- ICERs for pomalidomide compared with thalidomide plus dexamethasone and cyclophosphamide ranged from £65,400 (log-normal function to model overall survival) to £145,654 (Weibull function to model overall survival) per QALY gained.
- ICERs for pomalidomide compared with bendamustine plus thalidomide and dexamethasone ranged from £60,795 (log-normal function to model overall survival) to £133,890 (Weibull function to model overall survival) per QALY gained.

The company presented the results of a scenario analysis that limited the number of bortezomib cycles to 8 (as recommended in the summary of product characteristics). For pomalidomide compared with bortezomib plus dexamethasone, the company's economic model estimated incremental costs of £31,973 and incremental QALYs of 0.61, with an increase in the ICER from £50,366 (base case) to £52,325 per QALY gained.

3.23 The company presented results from 'weighted model averaging' probabilistic sensitivity analyses which accounted for the uncertainty around the choice of parametric curves. For pomalidomide compared with:

- bortezomib plus dexamethasone, the company estimated incremental costs of £30,231 and 0.596 incremental QALYs gained, with an ICER of £50,729 per QALY gained.

- thalidomide plus dexamethasone and cyclophosphamide, the company estimated incremental costs of £48,731 and 0.591 incremental QALYs gained, with an ICER of £82,503 per QALY gained.
- bendamustine plus thalidomide and dexamethasone, the company estimated incremental costs of £45,278 and 0.596 incremental QALYs gained, with an ICER of £76,031 per QALY gained.

At £50,000 per QALY gained, there is a 12.0% probability of pomalidomide being cost effective compared with all comparator technologies.

ERG comments on the clinical effectiveness

- 3.24 The Evidence Review Group (ERG) noted that the company's search strategies used filters which retrieved randomised controlled trials, observational studies and systematic reviews. Because the company's searches identified so few studies, the ERG reran the searches without the filters and retrieved 5000 records (compared with 1500 records with the filters). It then reviewed a sample of 100 records from the 3500 that were missed by the filters. It found that 31 of the 100 records met the company's inclusion criteria in terms of study design. The ERG noted that although most of these were prospective and retrospective case series, there were also 2 randomised controlled trials and 2 phase II single-armed studies. The ERG was concerned that the company may have excluded relevant evidence in its submission.
- 3.25 The ERG stated that comparing pomalidomide with high-dose dexamethasone is not relevant to the scope of the appraisal because clinicians do not consider dexamethasone as established practice in England, and therefore it was not listed as a comparator. The ERG agreed that dexamethasone is given mostly to reduce symptom severity after exhausting other active treatment options.
- 3.26 The ERG commented that, based on data from Gooding et al. (2013) and Tarant et al.(2013; see sections 3.9–3.11), the average life expectancy for people with relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib is 3.9–5.3 months with optimal care. However, despite dexamethasone being considered as a suboptimal treatment, patients in the control group of the MM-003 study achieved better outcomes than those

expected with optimal care (see section 3.5). The ERG concluded that the reasons for this unexpected result were not clear.

- 3.27 The ERG stated that the main limitation of the evidence submitted by the company was the lack of clinical-effectiveness data for the comparators listed in the scope. The ERG concluded that this leads to considerable uncertainty in quantifying the relative effectiveness of pomalidomide compared with each of the established treatment options in England.
- 3.28 The ERG commented that data for many patient characteristics were not published in the Gooding et al. (2013) and Tarant et al. (2013) studies. However, where data were available, patient characteristics in these studies and the MM-003 study were not similar. The ERG highlighted that, compared with patients in the Gooding et al. and Tarant et al. studies, patients in the pomalidomide group of the MM-003 study had received more prior myeloma therapies, were healthier in terms of the International Staging System score, were less likely to be treated with thalidomide and were more likely to have had stem cell transplantation. The ERG also noted that patients in Gooding et al. had longer disease duration than patients in MM-003 and Tarant et al. It also noted that patients' disease in Gooding et al. was less often refractory to bortezomib, lenalidomide and thalidomide compared with patients in the MM-003 study. The ERG concluded that the populations included in the 3 studies are not comparable.
- 3.29 The ERG considered that because patients in the MM-003 study were healthier in terms of International Staging System score, the technologies may have been more effective than if they had been studied in a population similar to that in Gooding et al. (2013). The ERG concluded that this could explain the relatively high effectiveness of high-dose dexamethasone in the MM-003 study (see section 3.26).
- 3.30 The ERG considered that the naïve indirect comparison of data from the MM-003 study with those from Gooding et al. (2013) and Tarant et al. (2013) was unreliable. For this reason, it asked the company during the clarification stage whether any studies were available that compared any comparator listed in the scope of this appraisal with high-dose dexamethasone in second- or

third-line relapsed and refractory multiple myeloma. If so, they would allow the company to create a network. Although the company stated that no such studies were available, the ERG noted that relevant studies may have been missed because of the filters in the company's search strategy.

ERG comments on the cost effectiveness

- 3.31 The ERG stated that the company's model structure was appropriate and similar to those used in previous NICE technology appraisals of treatments for multiple myeloma.
- 3.32 The ERG stated that the differences in baseline characteristics between patients in MM-003 and Gooding et al. (2013; see section 3.28) introduced considerable risk of bias when estimating the relative effectiveness of pomalidomide compared with the comparators. The ERG also highlighted the very small population size of the Gooding et al. study (n=30), which makes the estimate of relative effectiveness extremely uncertain. The ERG considered that the evidence to support the company's assumption that all comparators work equally well was weak (that is, the small Gooding et al. study, post hoc analyses of the MM-003 study and the company's expert opinion).
- 3.33 The ERG agreed that clinical plausibility is an important criterion when selecting the most appropriate parametric distribution with which to extrapolate. However, it noted that because the goodness of fit statistics were inconsistent for each outcome, it could not select a single distribution for each outcome as superior.
- 3.34 The ERG also made the following observations:
- Modelling an unlimited number of bortezomib cycles was not justified because the summary of product characteristics recommends a maximum of 8 cycles.
 - Administration costs for intravenous or subcutaneous injections were higher than the costs used in previous NICE technology appraisals.
 - The company's costs for medical resource use were appropriate.

- Not including costs relating to subsequent therapies was appropriate.

3.35 The ERG stated that despite the company's assumption of equal effectiveness for the comparators, a fully incremental analysis was appropriate because the company's assumption of equal effectiveness was not based on evidence, and their costs differed.

3.36 The ERG presented ICERs for several exploratory analyses using 'weighted model averaging' probabilistic sensitivity analyses (see sections 3.37–3.40).

3.37 The ERG stated that including dosing interruptions for pomalidomide in the model reduced costs considerably. It commented that the NHS may not be able to recover unused pomalidomide tablets from dosing interruptions in clinical practice. It noted that the company had also assumed that unused tablets for pomalidomide were not allowed to be recovered by the NHS (for example, when a patient reduces the dose). Therefore, the ERG conducted an exploratory analysis that removed the company's assumption that pomalidomide tablets were recovered from dosing interruptions by the NHS. For pomalidomide compared with:

- Bortezomib plus dexamethasone, the ERG estimated incremental costs of £35,525 and 0.587 incremental QALYs gained, with an ICER of £60,532 per QALY gained.
- Thalidomide plus dexamethasone and cyclophosphamide, the ERG estimated incremental costs of £54,210 and 0.582 incremental QALYs gained with an ICER of £93,214 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone, the ERG estimated incremental costs of £50,721 and 0.587 incremental QALYs gained, with an ICER of £86,486 per QALY gained.

3.38 The ERG stated that the use of the regression model to estimate utility values seemed appropriate. However, it considered that the disutility value for patients taking intravenous or subcutaneous therapies was uncertain; having been taken from NICE technology appraisal guidance on [erlotinib for the treatment of non-small-cell lung cancer](#), it applied to a different population (non-small-cell lung cancer) having different treatments. Moreover, the health state descriptions were valued using the EQ-5D visual analogue scale (which is not

in line with the NICE reference case). Because of this, the ERG conducted an exploratory analysis that assumed no disutility for taking intravenous or subcutaneous therapies. For pomalidomide compared with:

- Bortezomib plus dexamethasone, the ERG estimated incremental costs of £30,417 and 0.559 incremental QALYs gained, with an ICER of £54,415 per QALY gained.
- Thalidomide plus dexamethasone and cyclophosphamide, the ERG estimated incremental costs of £49,048 and 0.559 incremental QALYs gained, with an ICER of £87,752 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone, the ERG estimated incremental costs of £45,574 and 0.559 incremental QALYs gained, with an ICER of £81,527 per QALY gained.

3.39 The ERG stated that the company's economic model underestimated the effect of adverse reactions on health-related quality of life, because it converted the disutility values to reflect the weekly cycle length twice rather than once. The ERG conducted an exploratory analysis that corrected for this formulae error. For pomalidomide compared with:

- Bortezomib plus dexamethasone, the ERG estimated incremental costs of £29,814 and 0.568 incremental QALYs gained, with an ICER of £52,516 per QALY gained.
- Thalidomide plus dexamethasone and cyclophosphamide, the ERG estimated incremental costs of £48,555 and 0.561 incremental QALYs gained, with an ICER of £86,625 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone, the ERG estimated incremental costs of £45,048 and 0.568 incremental QALYs gained, with an ICER of £79,288 per QALY gained.

3.40 The ERG presented results for a scenario that combined all of its exploratory analyses (see sections 3.37–3.39). For pomalidomide compared with:

- Bortezomib plus dexamethasone, the ERG estimated incremental costs of £35,569 and 0.568 incremental QALYs gained, with an ICER of £62,681 per QALY gained.

- Thalidomide plus dexamethasone and cyclophosphamide, the ERG estimated incremental costs of £54,190 and 0.566 incremental QALYs gained, with an ICER of £95,818 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone, the ERG estimated incremental costs of £50,711 and 0.568 incremental QALYs gained, with an ICER of £89,229 per QALY gained.

3.41 The ERG commented that the results of the model validation checks done by the company were satisfactory (for example, the modelled median values were similar to the observed median values in MM-003 and Gooding et al. 2013). However, it stated that for each month of observed median progression-free survival, there was an increase in observed median overall survival of 3.37 months for pomalidomide (MM-003) and 2.01 months for the comparators (Gooding et al.). The ERG highlighted that these ratios differ from the 2.45-month increase in overall survival for each month of median progression-free survival reported by Felix et al. (2013), and are more favourable to pomalidomide. The ERG also noted that, based on the naïve indirect comparison of the pomalidomide data from the MM-003 study with the data from Gooding et al., the incremental median post-progression survival (6.1 months) seemed large compared with the incremental median progression-free survival (1.1 months). Therefore, the ERG did a deterministic scenario analysis in which it decreased post-progression costs and outcomes. For a scenario including the costs and QALYs from the progression-free health state only, the ERG estimated ICERs for pomalidomide compared with the comparator technologies of £685,476–1,237,288 per QALY gained. For a scenario that assumed a 50% decrease in post-progression costs and QALYs for both pomalidomide and its comparators, the ERG estimated ICERs for pomalidomide compared with the comparator technologies of £91,249–143,864 per QALY gained. The ERG concluded that if this sensitivity analysis had also included its proposed amendments to the company's economic model (see section 3.40), the ICERs reported for this scenario analysis would be much higher. Overall, the ERG concluded that considerable uncertainty exists in estimating the ICERs, and so the ERG was not comfortable in approximating a 'most plausible' ICER.

Company's additional evidence

3.42 The company provided additional evidence in its response to the Appraisal Consultation Document. These analyses had not been requested by the Committee and not agreed as per NICE's [guide to the processes of technology appraisals](#) because it was not expected that they would materially affect the recommendations. Therefore, they were not critiqued by the Evidence Review Group before they were presented to the Committee. The company presented revised estimates of clinical effectiveness that included the following:

- A more recent data cut from the MM-003 study (September 2013 rather than March 2013).
- Pooled progression-free survival and overall survival data from the phase II MM-002 study with data from the MM-003 study for the pomalidomide plus low-dose dexamethasone group (n=415 rather than n=302). The MM-002 study assessed pomalidomide (2 mg or 4 mg daily) with dexamethasone in patients with relapsed or refractory multiple myeloma. The company highlighted that because MM-002 included a population with 'less refractory' disease than MM-003, pooling the datasets ensured that enough patients with multiple myeloma not refractory to bortezomib and lenalidomide were included to allow for an 'adjusted' comparison with the data used for the comparators (see section 3.44).
- Pooled overall survival data from Gooding et al. (2013) and Tarant et al. (2013) for the comparators (n=56 rather than n=30).

Median progression-free survival was 4.0 months with pomalidomide and 2.6 months with the comparators (HR and 95% CI were not reported). Median overall survival was 13.6 months with pomalidomide and 6.5 months with the comparators (HR and 95% CI were not reported).

3.43 The company analysed the pooled Gooding et al. (2013) and Tarant et al. (2013) studies to support its assumption that the 3 comparator technologies had the same efficacy (see section 3.14). It compared the survival of patients who had bendamustine at fourth line with that of patients who had fourth-line treatment other than bendamustine. This log-rank test of a Kaplan–Meier curve showed no statistically significant differences ($p=0.9549$) between the overall

survival of patients who had bendamustine-containing regimens (n=20) and patients who did not have bendamustine-containing regimens (n=36). The company interpreted this as showing that bendamustine and other therapies are equally effective.

3.44 The company also revised its estimates for the relative effectiveness of pomalidomide compared with the comparators. The company adjusted the overall survival, progression-free survival and time-to-treatment failure outcomes to take into account factors that may have influenced the association between these outcomes and patients who had pomalidomide (MM-003), and patients who had current care (pooled Gooding et al. [2013] and Tarrant et al. [2013] dataset; see section 3.42). These potential confounding variables included age, disease duration, international staging system, being refractory to bortezomib, and being refractory to lenalidomide. The company stated that its adjusted analysis estimates the effectiveness for each treatment group in an 'equivalent patient population'. To extrapolate outcomes beyond the timeframe of the studies, the company fitted a series of parametric curves to the adjusted and pooled dataset using exponential, extreme-value, log-logistic, log-normal and Weibull distributions. In its revised base-case analysis, the company used the log-logistic function for each outcome (that is, time-to-treatment failure, progression-free survival and overall survival).

3.45 The company presented revised cost-effectiveness results that:

- included the revised estimates of relative effectiveness for pomalidomide compared with the comparators (see section 3.44)
- included a maximum of 8 bortezomib cycles in line with bortezomib's summary of product characteristics
- assumed the same administration costs for intravenous and subcutaneous therapies: that is, of a day-case admission (the company stated that this was consistent with NICE technology appraisal guidance on [bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation](#))

- assumed cost savings from dosing interruptions with pomalidomide (consistent with the company's original submission; see sections 3.16 and 3.37).

3.46 The company also presented revised deterministic ICERs for pomalidomide compared with:

- Bortezomib plus dexamethasone: 1.59 incremental life years gained (that is, 19.1 months), incremental costs of £51,265 and 0.91 incremental QALYs gained, with an ICER of £56,349 per QALY gained.
- Thalidomide plus dexamethasone and cyclophosphamide: 1.59 incremental life years gained, incremental costs of £65,491 and 0.91 incremental QALYs gained, with an ICER of £72,317 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone: 1.59 incremental life years gained, incremental costs of £61,131 and 0.91 incremental QALYs gained, with an ICER of £67,218 per QALY gained.

3.47 The company presented results from its revised 'weighted model averaging' probabilistic sensitivity analyses for pomalidomide compared with:

- Bortezomib plus dexamethasone: incremental costs of £48,462 and 0.79 incremental QALYs gained, with an ICER of £61,540 per QALY gained.
- Bendamustine plus thalidomide and dexamethasone: incremental costs of £57,004 and 0.79 incremental QALYs gained, with an ICER of £72,438 per QALY gained.

In its response to the Appraisal Consultation Document, the company did not present detailed results from its revised probabilistic sensitivity analyses comparing pomalidomide with thalidomide plus dexamethasone and cyclophosphamide, because the company considered that it has limited use in clinical practice. At £50,000 per QALY gained, the company estimated less than a 10% probability of pomalidomide being cost effective compared with all comparator technologies.

3.48 The company also presented the results of 3 scenario analyses:

- First, it explored a scenario that reduced the disutility for taking intravenous or subcutaneous therapies. In a scenario that set the disutility value for taking

intravenous or subcutaneous therapies to 0, the revised ICER for pomalidomide increased by £257 compared with bortezomib plus dexamethasone, and by £282 compared with bendamustine plus thalidomide and dexamethasone.

- Secondly, the company explored a scenario that included disutility values for grade 3 or 4 adverse reactions seen in 1% or more of patients taking pomalidomide in the MM-003 study (rather than 2% or more in its original base-case analysis). The company stated that including disutility values associated with adverse reactions in this way meant that only 1 additional adverse reaction was included (lower renal tract infection). In this scenario, the company estimated that the revised ICER for pomalidomide compared with bortezomib plus dexamethasone or bendamustine plus thalidomide and dexamethasone increased by between £17 and £104, depending on the unit cost used for treating lower renal tract infection.
- Thirdly, in a scenario changing the utility value in the progressed disease health state from 0.573 (original submission) to 0.536, the company estimated that the revised ICER for pomalidomide increased by £2529 compared with bortezomib plus dexamethasone and by £3018 compared with bendamustine plus thalidomide and dexamethasone.

3.49 Full details of all the evidence are [available](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pomalidomide, having considered evidence on the nature of relapsed and refractory multiple myeloma and the value placed on the benefits of pomalidomide by people with the condition, those who represent them and clinical experts. It also took into account the effective use of NHS resources.
- 4.2 The Committee heard from the clinical and patient experts about the nature of relapsed and refractory multiple myeloma. The Committee heard that relapse can follow a previously successful course of treatment, and that 'relapsed and refractory' refers to disease progression while on, or within 60 days after, a specific treatment. The Committee understood that multiple myeloma is an incurable disease, but that the introduction of thalidomide, bortezomib and lenalidomide has greatly improved survival and quality of life. The clinical expert stated that when patients have already had these multiple treatment options, they would benefit from novel treatment options. The patient experts highlighted the importance of having access to oral therapies: many current options for treatment are given intravenously or subcutaneously, which can cause unpleasant side effects (pain and trauma), may become difficult after years of injection therapy and may require periods of time away from home travelling to treatment centres. The Committee recognised the importance that both patients and physicians place on having novel and effective options available to treat multiple myeloma after consecutive relapses.
- 4.3 The Committee considered the likely position of pomalidomide in the treatment pathway for relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide. The Committee understood that at first diagnosis, autologous stem-cell transplantation with high-dose chemotherapy may be suitable for people in good health. When stem-cell transplantation is not suitable, NICE technology appraisal guidance on [bortezomib and thalidomide for the first-line treatment of multiple myeloma](#) recommends first-line triple therapy with thalidomide or bortezomib (the latter only in people unable to tolerate or with contraindications to thalidomide), an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid (prednisolone or

dexamethasone). For second-line treatment, NICE technology appraisal guidance on [bortezomib monotherapy for relapsed multiple myeloma](#) recommends bortezomib monotherapy as an option for people whose disease is at first relapse having had 1 prior therapy, and who have had (or are unsuitable for) bone marrow transplantation. In people who have had at least 2 prior therapies, NICE technology appraisal guidance on [lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy](#) recommends lenalidomide in combination with dexamethasone. The Committee was aware that the recommendation in NICE's technology appraisal guidance on lenalidomide for multiple myeloma after first-line bortezomib is currently under part-review. The Committee appreciated that pomalidomide may become a third-line option in England for patients unable to tolerate or who have contraindications to thalidomide. However, the clinical expert stated that pomalidomide plus low-dose dexamethasone is likely to be offered to most patients after a third relapse, but highlighted that fourth-line treatment (including pomalidomide) is only likely to be considered suitable for half of all patients with multiple myeloma.

- 4.4 The Committee considered the options available for treating multiple myeloma after third or subsequent relapse. The clinical and patient experts stated that there is no current best practice (this was supported by responses received to the Appraisal Consultation Document). In choosing a treatment, healthcare professionals together with the patient consider comorbidities, route of administration, and the response to and toxicity of previous treatments. For example, patients with peripheral neuropathy would be unlikely to have bortezomib a second time. The patient experts highlighted that there is currently no guidance from NICE or other professional organisations in England for relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide, and considered it an area of unmet need. The Committee understood from the clinical expert that patients in England can have pomalidomide through the Cancer Drugs Fund under specified circumstances. The clinical expert noted that other options included bendamustine used off-label, re-treating with bortezomib and conventional alkylating agents such as melphalan or cyclophosphamide, but highlighted that clinical practice varies. The clinical expert explained that, of these options, bendamustine is likely to be the most commonly prescribed in England, but this

was disputed in some responses received to the Appraisal Consultation Document. The Committee noted that in its submission, the company included these treatments as comparators. The Committee concluded that these treatments reflected clinical practice in England for relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide.

Clinical effectiveness

- 4.5 The Committee discussed the design of the MM-003 study. It recognised that the study was not blinded, and was concerned that this may have biased assessment of time to progression. However, the Committee heard from the clinical expert that this was unlikely because disease progression is determined biochemically. The Committee was also aware that progression was assessed by an Independent Response Adjudication Committee rather than by the treating clinician, and agreed that the assessment of outcomes by the Independent Response Adjudication Committee was appropriate in this case because the study was not blinded. The Committee discussed the choice of high-dose dexamethasone for the control group, highlighting that it did not represent an option for active treatment in England. The company explained that it chose high-dose dexamethasone after consulting with regulatory bodies, clinical experts and the trial's steering group, that no standard of care for treating relapsed and refractory multiple myeloma existed, and because at the time, high-dose dexamethasone was used for treating relapsed and refractory multiple myeloma. The clinical expert stated that because of its adverse effects, high-dose dexamethasone is now no longer an option for people whose disease has previously been treated with bortezomib and lenalidomide. The company confirmed that no studies were planned or ongoing to compare pomalidomide with any of the technologies used in clinical practice in the NHS (see section 4.4) in the population relevant for this appraisal. In response to the Appraisal Consultation Document, the company stated that it would be unethical to conduct a trial comparing pomalidomide with other comparators for relapsed and refractory multiple myeloma, because many comparators (for example, bendamustine) are off-label. However, the Committee was aware that high-dose dexamethasone as used in MM-003 does not have a marketing authorisation for this particular indication. The company also stated that any future trial comparing pomalidomide with current therapies would be

'unfeasible', because pomalidomide plus low-dose dexamethasone was 'standard practice'. The Committee was aware that bortezomib has a marketing authorisation as a re-treatment for treating relapsed and refractory multiple myeloma, and that since April 2013 bortezomib retreatment and bendamustine had been used through the Cancer Drugs Fund over 200 times each. A patient expert expressed his frustration that the company had not considered the needs of health technology assessment bodies when designing the MM-003 study. The Committee nevertheless recognised that the company had addressed the most relevant comparisons in its submission.

- 4.6 The Committee discussed the clinical-effectiveness data for pomalidomide from the MM-003 study. The Committee was concerned that the benefit from progression-free survival translated into a much larger benefit in overall survival, even though patients stopped taking pomalidomide after disease progression. The Committee heard from the clinical expert that because progression in multiple myeloma is assessed biochemically, it may precede the time when the disease becomes symptomatic; that is, progression-free survival is diagnosed much earlier in multiple myeloma than in many other cancers. The Committee was satisfied with responses to the Appraisal Consultation Document showing that a similar ratio of post-progression survival to progression-free survival had been observed in the MM-003 study and in other NICE technology appraisals of drugs for multiple myeloma. The Committee noted that the overall survival benefit relative to the progression-free survival benefit was more pronounced with pomalidomide than with high-dose dexamethasone. The clinical expert cited differences between the drugs' adverse effects and mechanisms of actions, particularly that pomalidomide is immunomodulatory and so may lead to fewer infections after treatment has stopped. The Committee concluded that the benefit in the post-progression phase relative to the progression-free phase was plausible.
- 4.7 Because pomalidomide was given in combination with low-dose dexamethasone but compared with high-dose dexamethasone in the MM-003 study (rather than compared with low-dose dexamethasone), the Committee was concerned that the benefits of pomalidomide may have been overestimated because of potential harmful effects of high-dose dexamethasone. The Committee heard from a patient expert that a trial

comparing lenalidomide plus low-dose dexamethasone with lenalidomide plus high-dose dexamethasone suggested that lenalidomide plus low-dose dexamethasone was more effective. The Committee concluded that because of the design of the MM-003 study, the extent of the benefits associated with pomalidomide itself was uncertain, and that the MM-003 results were of limited value in comparing pomalidomide with 'established practice without pomalidomide' as specified in the scope of this appraisal.

- 4.8 The Committee discussed the clinical-effectiveness data submitted by the company for the comparators (bortezomib plus dexamethasone, thalidomide plus dexamethasone and cyclophosphamide, and bendamustine plus thalidomide and dexamethasone). The Committee was concerned that the company may have missed relevant evidence because of the filters used when searching the literature, and only identified data from small retrospective observational studies. The Committee was aware of 3 registries that may be relevant to the decision problem: the Connect multiple myeloma registry (NCT01081028), the Haematological Malignancy Research Network (HMRN) registry, and the Slone myeloma registry. The Committee was aware that the Connect registry was owned by the company, and that only a brief overview of the HMRN registry had been included by the company in its submission. The Committee heard from the company that compared with the Gooding et al. (2013) study, the HMRN registry data enrolled fewer patients (n=17) and were unlikely to be representative of clinical practice because none of the patients had either bendamustine- or bortezomib-containing regimens. In its response to consultation, the company stated that data for patients at the stage of the treatment pathway relevant to this appraisal had not yet been reported from the Connect registry despite enrolment starting in 2009 because it recruited only newly diagnosed patients. The company also explained that it had omitted data from the now-closed Slone registry (which the company financially supported) because it stopped collecting outcome data before patients had fourth-line treatment. The Committee was also aware that between April 2013 and June 2014, approximately 500 patients in England had access to retreatment with bortezomib or to bendamustine for relapsed and refractory multiple myeloma through the Cancer Drugs Fund under specific circumstances. It heard from the company that outcome data were not available from the Cancer Drugs Fund or from the Systemic Anti-Cancer

Therapy database, managed by the National Cancer Intelligence Network under the auspices of Public Health England. The Committee heard from the company that it had contacted 11 'key opinion leaders' in England to get patient-level data for relapsed and refractory multiple myeloma, but that only data from the Gooding et al. study were available at the time of its original submission. The company obtained patient-level data from the Tarant et al. (2013) study after the first appraisal committee meeting, but the data included mortality only and did not provide further evidence on disease progression or time-to-treatment failure.

- 4.9 The Committee discussed the Gooding et al. (2013) and Tarant et al. (2013) studies in comparison with MM-003. It understood from the clinical experts that in clinical practice approximately 70% of patients with multiple myeloma are aged over 65 years, but in the MM-003, Gooding et al. and Tarant et al. populations this proportion was closer to 50%. The Committee acknowledged from the company's response to the Appraisal Consultation Document that the relevant patient population for this appraisal represents a late-line subset of all multiple myeloma patients, and only for half of patients is fourth-line treatment expected to be considered suitable. These patients are likely to be the physically fitter (and therefore typically younger) than other patients, explaining the lower proportion of patients aged over 65 years in the studies. The Committee raised a number of other concerns about the Gooding et al. study, including that it was published only as a poster presentation, the analysis was based on the results of patients from a single centre, and it provided limited details on how the authors selected the 30 patients and how their baseline characteristics compared with those of the wider multiple myeloma population of patients from which the 30 were chosen. The Committee understood that the company financially supported the Gooding et al. study and had access to the data. The Committee recognised that the study's authors had acknowledged the uncertainty associated with the results, pointing out the authors' statement that 'the sample size was too small to obtain definitive progression-free survival or overall survival conclusions'. The Committee also observed that the control group of MM-003 (who had 'suboptimal' treatment with high-dose dexamethasone) lived longer than patients described in both Gooding et al. and Tarant et al., which it noted seemed counterintuitive. In its response to consultation, the company stated

that this observation was plausible because the control group of the MM-003 study reflected current care in that patients only had high-dose dexamethasone for a short time before going on to have treatments that constitute established practice. However, the Committee considered that because the evidence available for patients with current care was not robust, it was no more able to compare high-dose dexamethasone from the MM-003 study with current care than it was to compare the pomalidomide group from the MM-003 study with current care. The Committee was aware that the Evidence Review Group (ERG) considered patients in the MM-003 study to be healthier than those in Gooding et al. because they had disease of a shorter duration, appeared to have an earlier stage of the disease (as classified by the International Staging System) and were more likely to have had stem cell transplantation. The Committee heard from the clinical expert that disease stage and duration may influence prognosis. It then heard that the company considered the 30 patients described by Gooding et al. to be healthier than those in MM-003 because they had had fewer therapies. The Committee noted that the differences in populations may influence outcomes, but it was not clear if the differences favoured pomalidomide or current treatments (that is, the direction of confounding). Because of the limitations in the evidence presented by the company, the Committee reiterated its conclusion that it was not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options (see section 4.8).

- 4.10 The Committee considered the safety data from the MM-003 study. It noted that the proportion of patients with adverse reactions were similar between those taking pomalidomide and high-dose dexamethasone. The Committee commented that the most common grade 3 or 4 adverse reactions reported in patients taking pomalidomide were neutropenia, anaemia and thrombocytopenia. The Committee heard from the clinical expert that the side effects associated with pomalidomide are generally manageable by reducing or interrupting the dose. The patient expert highlighted that patients appreciate that pomalidomide is taken orally and that it has manageable side effects. The Committee concluded that, although pomalidomide can lead to several different adverse reactions, it is generally well tolerated.

Cost effectiveness

- 4.11 Despite the Committee's concerns about the evidence for the relative effectiveness of pomalidomide, it considered the company's economic models (from both its original submission and additional analyses provided during consultation) and the ERG's critique of the company's original cost-effectiveness results. The Committee commented that comparing the modelled curves with the Kaplan–Meier plots for overall survival appeared to show that in the original model, survival for pomalidomide may have been overestimated and survival for the comparators may have been underestimated (for all distributions). The Committee heard that the company updated its economic model in its response to consultation to include progression-free survival and overall survival data for pomalidomide from September 2013 (rather than March 2013 as included in its original economic model). The Committee considered it appropriate to include these more mature data. It was also aware that the company had included more patient-level data to model outcomes for patients taking pomalidomide and comparators in its response to consultation. However, the Committee noted that the sample size for the 'pooled' comparator group was still small with the inclusion of survival data from Tarant et al. (2013, see [section 3.42](#)). Furthermore, the Committee acknowledged that after consultation the company had attempted to adjust for differences in patient characteristics between the comparator group (pooled Gooding et al. and Tarant et al. data) and pomalidomide group (pooled MM-002 and MM-003 data). The Committee was aware that the sample size for comparators was small, and the number of events even smaller. Therefore, the Committee was concerned that the model may contain too many predictors relative to the number of events, which may lead to problems such as 'over-fitting' the data. The Committee also recognised the risk of residual confounding because other patient characteristics associated with mortality were not included in the company's adjusted analysis. The company acknowledged the possibility of incomplete control of confounding, noting that it could adjust only for covariates for which it had information. The Committee appreciated that the company had made efforts to respond to its concerns, but the results of the adjusted analysis did not establish with any more certainty the magnitude of the relative effectiveness of pomalidomide compared with 'established clinical practice without pomalidomide'.

- 4.12 The Committee discussed the company's choice of a log-logistic function to extrapolate overall survival data. Having considered an analysis presented by the ERG estimating the proportions of people alive over time in the company's original model, the Committee determined that the log-logistic distribution may have overestimated long-term survival. However, it heard from the clinical expert that a very small proportion of patients may live for a long time (that is, up to 25 years). The clinical expert estimated that, based on his personal experience, around 10% of people with relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide may be alive at 5 years with current care. The Committee heard from the patient expert that this was reasonable, because patients would continue to have other therapies after fourth-line treatment. The Committee noted that the proportion of patients alive in the comparator group was even lower in the company's revised economic model (2.1%) than in its original economic model (4%). The Committee heard that the company interpreted the clinical and patient experts' views on the matter (that around 10% of people with relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide may be alive at 5 years and having current care) as pertaining to the overall multiple myeloma population, rather than the relapsed and refractory multiple myeloma population. The Committee acknowledged that 10% was an approximate value, but reiterated its original concern that the proportion of patients alive at 5 years and having current care in the company's economic original model appeared too low. The Committee concluded that the company's model, for all parametric functions chosen, underestimated the survival of patients in the comparator group.
- 4.13 The Committee discussed the company's assumption that the 3 comparator technologies have the same efficacy. The company based this on its post hoc analysis of 66 patients in the MM-003 study, which showed no statistically significant differences between post-progression survival and 7 different treatment regimens given after disease progression, and from similar analyses of the 30 patients in the Gooding et al. (2013) study. In response to consultation, the company submitted an additional analysis of 56 patients (see [section 3.43](#)) and the Committee heard from the company that this further supported that there was no evidence to suggest that the efficacy of comparators differs. However, the Committee agreed that the analyses

included too few patients to support the company's assumption of equal effectiveness. The Committee heard from the clinical expert that the 3 comparators included in the company's submission could not be considered equally effective, and that this assumption could be supported only with more robust evidence. The Committee concluded it was not reasonable for the company to assume that the comparators in the economic model were equally effective.

- 4.14 The Committee discussed how well the company's model predicted survival after patients' disease had progressed. The Committee was concerned that the company's original model predicted that, relative to the 3 comparators, most of the survival benefits for patients taking pomalidomide were gained after disease progression. The Committee acknowledged that, compared with re-treating using previously used treatments, pomalidomide's mode of action may offer extra benefits after treatment stops, such as fewer infections and prolonged survival (see section 4.6). However, a higher proportion of patients had disease that responded to treatment in Gooding et al. (2013) than in the pomalidomide group of MM-003; but the Committee heard from the company that this may be because the 2 studies used different criteria to define response. The Committee was persuaded that the size of post-progression survival relative to progression-free survival in MM-003 and comparator studies was broadly consistent with studies included in previous NICE technology appraisals for multiple myeloma. However, the Committee was concerned that almost all of the overall survival benefits estimated in the company's original model occurred once patients stopped treatment (that is, post-progression) – 96% of the incremental survival – and that this was implausible. The company stated that it had attempted to address this disparity, and that its revised economic model estimated the post-progression benefit to constitute 79% of the incremental survival. The Committee acknowledged that the company had attempted to explore this uncertainty but highlighted that this was based on the company's adjusted analysis and comparator data (Gooding et al. [2013] and Tarant et al. [2013]) which the Committee concluded were extremely weak. The Committee noted that the modelled mean overall survival benefit was 12.7 months (company's original model), and 19.1 months (company's revised model). The Committee concluded that in the light of the uncertain and very weak comparator data both these values were likely to be considerable

overestimates of the true mean overall survival benefit, and agreed that it was more appropriate for the company to present more clinically plausible, smaller estimates of incremental survival in the model.

- 4.15 The Committee discussed the company's assumptions around treatment costs in its economic model. First, the Committee noted that the company used the same cost for administering intravenous and subcutaneous therapies, whereas the Committee considered that subcutaneous therapies may be less expensive to administer. Having acknowledged that the company's approach was consistent with the submission for NICE technology appraisal guidance on [bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation](#), the Committee noted that lowering the cost for subcutaneous administration would likely have only a small impact on the estimated incremental cost-effectiveness ratios (ICER). Secondly, the Committee commented that it is more appropriate to limit the number of bortezomib cycles to 8 in line with the summary of product characteristics. The Committee was aware that having fewer bortezomib cycles increased the ICER for pomalidomide by about £2000 per quality-adjusted life year (QALY) gained in the company's original economic model (see [section 3.22](#)). Thirdly, the Committee discussed whether it was appropriate for the company to assume cost savings from treatment interruptions because patients could take unused pomalidomide tablets later when they re-start treatment. The clinical expert explained that unused tablets from treatment interruptions would not be recoverable in clinical practice because patients would generally follow the same prescription cycle, nor would NHS pharmacists reissue unused tablets to other patients. The Committee also highlighted that the NHS incurs the full cost of a pack of pomalidomide tablets before a patient interrupts treatment, and therefore it was not certain whether any related cost savings would be made by the NHS. The Committee recognised that if all 3 of these adjustments had been accounted for in the company's economic model, the ICERs would increase for all comparisons.
- 4.16 The Committee discussed the company's approach to estimating health-related quality of life in people with relapsed and refractory multiple myeloma. The Committee appreciated that the company had included EQ-5D data from the MM-003 study as preferred by NICE in its [guide to the methods](#)

[of technology appraisals](#) (2013). The Committee heard that the company's regression analysis accounted for the imbalance between the number of responses to the EQ-5D questionnaire it had from patients in better health relative to those in poorer health. The Committee was aware that EQ-5D data were collected only until treatment stopped in MM-003 (that is, early in the course of disease progression). The Committee was therefore concerned that the company overestimated the utility value for the progressed disease health state, because the EQ-5D data collected in MM-003 were not likely to reflect the 'average' health-related quality of life for the entire time in progressed disease before death. The Committee considered that the company's revised, slightly lower, utility value for the progressed disease health state included in its response to the Appraisal Consultation Document better reflected the 'average' health-related quality of life of progressed disease than the utility value used in its original submission. The Committee highlighted that the revised utility value for the progressed disease health state increased the ICERs estimated by the company's economic model for pomalidomide compared with each of the 3 comparators. The Committee concluded that it was more appropriate for the economic model to include the lower utility value because it was likely to be more valid than the value submitted by the company in its original submission.

- 4.17 The Committee discussed the disutility values included in the company's economic model. The company could not justify why it chose to include disutility values only for adverse reactions that occurred in more than 2% of patients taking pomalidomide. The Committee considered that this cut-off point was arbitrary, and was uncertain about the effect that including disutilities from all adverse reactions would have on the ICERs, although it acknowledged that the company's ICERs were relatively insensitive to changes in the disutility values for some adverse events. The Committee understood that the company included the same disutility value for intravenous and subcutaneous treatments. It agreed that a patient's health-related quality of life is generally higher with oral therapy than with intravenous or subcutaneous therapy, but the degree of benefit was uncertain. The Committee disagreed that the disutility associated with subcutaneous therapy was the same as that for intravenous therapy, because subcutaneous treatments are generally less problematic for patients. The Committee concluded that the company's arbitrary criteria for

including adverse reactions and the assumption of equal disutility for intravenous and subcutaneous therapies were not appropriate, but agreed that alternative assumptions would have minimal impact on the estimated ICER.

4.18 The Committee discussed the ICERs presented for pomalidomide plus low-dose dexamethasone compared with 'established practice without pomalidomide' for treating relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. The Committee agreed that the analyses should not assume cost savings from interrupting pomalidomide treatment (see section 4.15) and that the corrected calculation of disutility associated with adverse reactions should be used (see [section 3.39](#)). However, the Committee disagreed with the ERG's approach of excluding a health-related quality of life benefit associated with taking oral therapies rather than intravenous or subcutaneous therapy (see [sections 3.38](#) and 4.17). The Committee considered any ICER to be highly uncertain, given that estimate of relative effectiveness was assumed to be the same for all comparisons and was based on a naive indirect comparison (and associated potential biases; see sections 4.8–4.9 and 4.11–4.13). The Committee highlighted that the additional analyses, through which the company attempted to address some of the uncertainties, did not adequately reduce the uncertainty or provide more robust evidence. Moreover, the Committee noted that a scenario was not presented by the company that combined and addressed the further uncertainty with respect to:

- the company's model underestimating overall survival in the comparator group (see section 4.12)
- the implausible magnitude of survival benefits in the post-progression phase estimated by the company's model (see section 4.14)
- presenting more clinically plausible, smaller estimates of incremental survival in the model (see section 4.14)
- the utility value for the progressed disease health state (see section 4.16).

The Committee was of the view that the ICERs for pomalidomide would be more

likely to increase than to decrease if the company had accounted for these uncertainties.

- 4.19 The Committee acknowledged that all ICERs presented by both the company and the ERG were over £50,000 per QALY gained for pomalidomide compared with bortezomib. The Committee highlighted that the clinical expert and responses to the Appraisal Consultation Document broadly suggested that although there is no standard of care for people with relapsed and refractory multiple myeloma, bendamustine is likely to be the most commonly used therapy in this setting in England (see section 4.4). When comparing pomalidomide with bendamustine plus thalidomide and dexamethasone, all ICERs presented were over £70,000 per QALY gained. The Committee concluded that, even without including all of the Committee's preferred assumptions, using either of the company's approaches to establish the relative effectiveness estimated ICERs that were higher than what is normally considered a cost-effective use of NHS resources.
- 4.20 The Committee discussed the innovative nature of pomalidomide and whether the economic analysis had captured all changes in health-related quality of life. In its submission, the company stated that pomalidomide addresses an unmet need for an effective fourth-line treatment for relapsed and refractory multiple myeloma. The company highlighted that some current options are administered intravenously (bendamustine, bortezomib) or subcutaneously (bortezomib) in hospital. The Committee agreed that pomalidomide is easy to take and usually well tolerated. It also highlighted that most of the options currently offered in this setting involve re-treating with previously used drugs, and recognised that patients may benefit from drugs with a new mechanism of action at this stage of the disease. However, the Committee concluded that these benefits were captured within the company's economic modelling.
- 4.21 The Committee considered supplementary advice from NICE, which 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 of 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.
- The technology is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

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 of the economic modelling are plausible, objective and robust.

- 4.22 The Committee discussed whether pomalidomide plus low-dose dexamethasone fulfilled the criteria for a life-extending end-of-life treatment. The Committee noted that the median overall survival of patients with relapsed and refractory multiple myeloma previously treated with bortezomib and lenalidomide, despite being from different populations, was shorter than 24 months and ranged from 3.9 and 5.3 months based on the Gooding et al. (2013) and Tarant et al. (2013) studies to 8.1 months in the control group of MM-003. The Committee considered that the company's model underestimated the mean overall survival for the comparators (see section 4.12), but agreed it reasonable to assume that pomalidomide is indicated for patients with a short life expectancy. The Committee understood that the company had estimated a patient population of 669 in England, and the ERG noted that this was a reasonable estimate. The Committee was satisfied that pomalidomide was indicated for a small patient population.
- 4.23 The Committee considered whether pomalidomide treatment extends life by at least 3 months compared with current NHS treatment. The Committee noted that in the MM-003 trial the differences in median overall survival between pomalidomide and high dose dexamethasone were 4.4 months (unadjusted for crossover), and 6 to 7 months when adjusted for crossover (see [section 3.5](#)). The Committee noted that when compared with the relevant comparators and based on a naive indirect comparison of data from the studies

(see [section 3.42](#)), the difference in the median overall survival was 7.1 months while the estimates of the difference in the mean overall survival from the economic model were 12.7 months (original model) and 19.1 months (revised economic model). The Committee noted that high-dose dexamethasone was not a relevant comparator for pomalidomide in the population in this appraisal, but heard that the company and consultees considered that the control group of the MM-003 study reflected current care, in part because patients were treated with high-dose dexamethasone only for a short time before then having other treatments that constitute established practice. However, the Committee considered that because the evidence presented for patients having current care was extremely weak and liable to confounding bias (section 4.11), it was no more able to compare high-dose dexamethasone from the MM-003 trial with current care than it was to compare the pomalidomide group from the MM-003 study with current care. The Committee highlighted its conclusion that it was not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options (see sections 4.9 and 4.11) based on the available evidence provided before and after consultation (see section 4.19). However, bearing in mind the magnitude of the differences in the overall survival estimates between pomalidomide and high dose dexamethasone, the Committee considered it probable that pomalidomide would lead to a mean extension of life of 3 months or more. If overall survival with pomalidomide plus low-dose dexamethasone approximates 12.7 months as in the MM-003 trial, the survival with standard care would have to be 9.7 months or less to provide a 3-month overall survival difference. Although not considered robust, all data presented to the Committee for comparators indicated life expectancies shorter than 9.7 months. For this reason, the Committee was persuaded that pomalidomide extends life for at least 3 months on average when compared with standard NHS care. However, considering the currently presented ICERs, the Committee concluded that even with the end-of-life criteria met, the weighting that would have to be placed on the QALYs gained would be too high to consider pomalidomide a cost-effective use of NHS resources. Also, the Committee concluded that the uncertainty in the relative effectiveness of pomalidomide compared with established NHS practice would affect any weighting that could be placed on the QALYs gained.

Summary of Appraisal Committee's key conclusions

TA338	Appraisal title: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib	Section
Key conclusion		
<p>Pomalidomide, in combination with dexamethasone, is not recommended within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults who have had at least 2 prior treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.</p> <p>This is because all ICERs for pomalidomide presented were over £50,000 per QALY gained compared with bortezomib, and over £70,000 per QALY gained compared with bendamustine plus thalidomide and dexamethasone, and would further increase when a number of more realistic assumptions were included in the model. The Committee also noted that there was substantial uncertainty about the relative effectiveness of pomalidomide compared with current care.</p>		1.1, 4.18, 4.19, 4.9
Current practice		
Clinical need of patients, including the availability of alternative treatments	Multiple myeloma is an incurable disease, but the introduction of thalidomide, bortezomib and lenalidomide has greatly improved survival and quality of life. The clinical expert stated that when patients have already had these treatments, they would benefit from novel treatment options. The Committee recognised the importance that both patients and physicians place on having novel and effective options available to treat multiple myeloma after consecutive relapses.	4.2
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee agreed that pomalidomide is easy to take and usually well tolerated. It also highlighted that most of the options currently offered in this setting involve re-treating with previously used drugs, and recognised that patients may benefit from drugs with a new mechanism of action at this stage of the disease.</p>	<p>4.2</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The clinical expert stated that pomalidomide plus low-dose dexamethasone is likely to be offered to most patients after a third relapse, but highlighted that only half of patients with multiple myeloma are likely to be considered suitable for fourth-line treatment (including pomalidomide).</p>	<p>4.3</p>
<p>Adverse reactions</p>	<p>The Committee concluded that, although pomalidomide can lead to several different adverse reactions, it is generally well tolerated.</p>	<p>4.10</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The Committee highlighted that high-dose dexamethasone, used in the MM-003 study for the control group, did not represent an option for active treatment in England.</p> <p>The Committee understood that the company had made substantial efforts to retrieve evidence on comparators relevant to the appraisal, but that robust data were not available at the moment.</p>	<p>4.5, 4.8</p>

<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee raised a number of concerns about the Gooding et al. study, including that the analysis was based on the results from a single centre, and it provided limited details on how the authors selected the 30 patients and how their baseline characteristics compared with those of the wider multiple myeloma population.</p>	<p>4.9</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee concluded that the data submitted by the company were inadequate to establish with any certainty the relative effectiveness of pomalidomide compared with 'established clinical practice without pomalidomide'.</p> <p>Gooding et al. stated that 'the sample size was too small to obtain definitive progression-free survival or overall survival conclusions'.</p> <p>The Committee also observed that the control group of MM-003 living longer than patients described in both Gooding et al. and Tarant et al., seemed counterintuitive. In its response to consultation, the company stated that this observation was plausible because the control group of the MM-003 study reflected current care in that patients only had high-dose dexamethasone for a short time before going on to have treatments that constitute established practice. However, the Committee considered that because the evidence available for patients with current care was not robust, it was no more able to compare high-dose dexamethasone from the MM-003 study with current care than it was to compare the pomalidomide group from the MM-003 study with current care.</p>	<p>4.8, 4.9</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>N/A</p>	

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Because of the limitations in the evidence presented by the company, the Committee reiterated its conclusion that it was not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options.</p>	<p>4.9</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company developed a semi-Markov partitioned survival model which 4 health states: progression-free disease, split into 'on treatment' and 'off treatment'; progressed disease; and death.</p>	<p>3.13</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The company's model underestimated the survival of patients in the comparator group.</p> <p>It was not possible to state that the comparators were equally effective.</p> <p>The Committee acknowledged that the company had attempted to explore the size of the post-progression benefits estimated by the company's model but highlighted that this was based on the company's adjusted analysis and comparator data, which the Committee concluded were extremely weak.</p> <p>The Committee concluded that in the light of the uncertain and very weak comparator data, both these values were likely to overestimate the true mean overall survival benefit, and agreed that it was more appropriate for the company to present more clinically plausible, smaller estimates of incremental survival in the model.</p> <p>The Committee concluded that it was more appropriate for the economic model to include the revised, slightly lower, utility value because it was more likely to be valid than the value submitted by the company in its original submission.</p>	<p>4.12, 4.13, 4.14</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee appreciated that the company had included EQ-5D data.</p> <p>The Committee concluded that changes in health-related quality-of-life were captured within the company's economic modelling.</p>	<p>4.16, 4.19</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>N/A</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>No specific discussion on key drivers because of the uncertainties around, and plausibility of, the assumptions and inputs in the company's economic model'.</p>	
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>ICERs presented for pomalidomide were over £50,000 per QALY gained compared with bortezomib, and over £70,000 per QALY gained compared with bendamustine plus thalidomide and dexamethasone.</p> <p>The Committee were of the view that the ICERs for pomalidomide would be more likely to increase than to decrease if the uncertainties were accounted for in the economic analysis.</p>	<p>4.18, 4.19</p>

Additional factors taken into account		
Patient access schemes (PPRS)	N/A	
End-of-life considerations	<p>The Committee was satisfied that pomalidomide was indicated for a small patient population with a life expectancy of less than 24 months.</p> <p>The Committee was not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options based on the available evidence provided before and after consultation. However, bearing in mind the magnitude of the differences in the overall survival estimates between pomalidomide and high dose dexamethasone in the trial, and all data presented to the Committee for comparators, the Committee was persuaded that pomalidomide extends life for at least 3 months on average when compared with standard NHS care.</p>	4.22, 4.23
Equalities considerations and social value judgements	Potential equality issues raised during the appraisal were outside the remit of NICE technology appraisal guidance.	

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review by the Guidance Executive 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
March 2015

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Jeff Aronson

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

Professor John Cairns

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

Mr Matthew Campbell-Hill

Lay member

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Dr Maria Dyban

General Practitioner, Cardiff

Mr Robert Hinchliffe

Higher Education Funding Council for England Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Professor Daniel Hochhauser

Consultant in Medical Oncology, University College London Cancer Institute

Dr Neil Iosson

Locum General Practitioner

Mrs Anne Joshua

NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Ms Emily Lam

Lay member

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Mr Christopher O'Regan

Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Mr Cliff Snelling

Lay member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke

Technical Lead

Jeremy Powell

Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Tomini F, Joore M et al., Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib, August 2014.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. 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. Company/sponsor:

- Celgene

II. Professional/specialist and patient/carer groups:

- Cancer Research UK
- Myeloma UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

-
- Department of Health, Social Services and Public Safety for Northern Ireland
 - Healthcare Improvement Scotland
 - Janssen
 - National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on pomalidomide by attending the initial Committee discussion and providing a written evidence statement to the Committee. They were also invited to comment on the ACD.

- Dr Matthew Streetly, Consultant Haematologist, Guy's Hospital, nominated by the Royal College of Physicians – clinical expert
- Judy Dewinter, Chair of Myeloma UK, nominated by Myeloma UK – patient expert
- Eric Low, Chief Executive of Myeloma UK, nominated by Myeloma UK – patient expert

D. Representatives from the following company/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Celgene

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE [single technology appraisal](#) process.

It has been incorporated into the NICE pathway on [blood and bone marrow cancers](#) along with other related guidance and products.

We have produced [information for the public](#) explaining this guidance. [Tools](#) to help you put the guidance into practice and information about the [evidence](#) it is based on are also available.

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This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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