The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pomalidomide in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the evaluation report).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using pomalidomide in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 5th November 2014

Second Appraisal Committee meeting: 19th November 2014

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

1  Appraisal Committee’s preliminary recommendations

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 currently receiving treatment initiated within the NHS with pomalidomide that is not recommended for them by NICE in this guidance 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 8) considered evidence submitted by the manufacturer of pomalidomide and a review of this submission by the Evidence Review Group (ERG; section 9).

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 were 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. They 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, 146 patients (48.7%) in the pomalidomide group died compared with 84 patients (56.0%) in the dexamethasone group.

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 grade 5 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
• bortezomib plus dexamethasone
• thalidomide plus dexamethasone and cyclophosphamide
• bendamustine plus thalidomide and 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 technologies 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 as 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
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 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 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, the majority 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 company’s assumption that all comparators work equally well was not supported by the evidence from the Gooding et al. study, post hoc analyses of the MM-003 study and 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 of 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 a fully incremental analysis was appropriate because the company only assumed that the comparators had equal efficacy (that is, 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. Full details of all the evidence are in the committee papers.

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 happen following 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 only half of patients with multiple myeloma are likely to be considered for fourth-line treatment (including pomalidomide).

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. 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 national bodies 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 and re-treating with bortezomib or with 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. 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 considered 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. However, the Committee highlighted that the company would have been aware that other (novel) treatments existed, and could have included another treatment group in its trial. The clinical expert stated that because of its adverse effects, high-dose dexamethasone is not 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. A patient expert expressed their frustration that the company had not considered the needs of health technology assessment bodies when designing the MM-003 study. The Committee recognised that
the company had addressed the most relevant comparisons in its submission, and concluded that comparing pomalidomide with high-dose dexamethasone was not relevant to this appraisal.

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, that progression-free survival is diagnosed much earlier in multiple myeloma than in many other cancers. 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 but not without uncertainty for pomalidomide compared with high-dose dexamethasone.

4.7 Because pomalidomide was given in combination with low-dose dexamethasone, the Committee recognised that any difference in effectiveness between the 2 groups of the MM-003 study may be related to the benefit of low-dose over high-dose dexamethasone (rather than pomalidomide itself). 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 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 first registry (Connect) was owned by the company, and that the second (HMRN) had been included by the company in its submission to the Scottish Medicines Consortium. The Committee heard from the company that it had not included the HMRN registry data because it enrolled fewer patients (n<30) than the Gooding et al. (2013) study. The company also explained that data from the Connect registry had not yet been reported, but the Committee did not consider this an adequate reason for not including it because the registry had recruited patients since 2009. The company was also unable to explain to the Committee why data from the now-closed Slone registry had been omitted. The Committee considered that it would have been appropriate to include these registries. 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. The company explained that it considered the Gooding et al. and Tarant et al. (2013) studies to be the most relevant to the decision problem of the appraisal. However, the Committee concluded that it would have been more appropriate to provide more data to establish the relative effectiveness of pomalidomide.

4.9 The Committee discussed the Gooding et al. (2013) and Tarant et al. (2013) studies in comparison with MM-003. It understood 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 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. However, 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 concluded that the differences in populations may influence outcomes, but it was not clear if they favoured pomalidomide (that is, the direction of confounding). Because of the limitations in the evidence that the company presented, the Committee was not able to judge with any confidence whether pomalidomide is more effective than the current treatment options.

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 model and the ERG’s critique of the company’s cost-effectiveness results. The Committee commented that comparing the modelled curves with the Kaplan–Meier plots for overall survival appeared to show that survival for pomalidomide may have been overestimated and that survival for the comparators may have been underestimated (for all distributions). The Committee heard that the company chose to use overall survival data from March 2013 (the final analysis of progression-free survival), despite having overall survival data up to September 2013. The Committee considered that omitting these more mature data added to the uncertainty about the overall survival of patients taking pomalidomide. Furthermore, the Committee was concerned that the company had made no attempt to adjust for differences in patient characteristics between Gooding et al. and the MM-003 study. The Committee concluded that it would have preferred the company to use more mature data and to adjust for potential confounders (differences in baseline characteristics) of the association between treatments and survival.

4.12 The Committee discussed the company’s choice of a log-logistic function to extrapolate overall survival data from the MM-003 study and Gooding et al. (2013). Having considered an analysis presented by the ERG on the proportions of people alive over time in the company’s 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
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-person Gooding et al. (2013) study. The Committee agreed that the company had provided weak and possibly underpowered data to support its assumption, and that its analyses were unlikely to find real differences that may exist. 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 such an assumption could only be supported with more evidence. The Committee concluded it was not possible to state with any certainty that the comparators were equally effective.

4.14 The Committee discussed survival after patients’ disease had progressed as predicted by the company’s model. The Committee was concerned that the company’s model predicted that, relative to the 3 comparators, most of the survival benefits for patients taking pomalidomide were gained after disease progression (incremental pre-progression survival of 0.042 years and incremental post-
progression survival of 1.018 years). 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 (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. The Committee heard from the company that the size of post-progression survival benefits relative to progression-free survival was consistent with previous NICE technology appraisals in multiple myeloma, but provided no specific comparisons. However, the Committee commented that the size of the post-progression benefits estimated by the company’s model – some 96% of the incremental survival – was implausible. The Committee concluded that post-progression survival benefit as estimated by the company’s economic model for pomalidomide compared with ‘established practice without pomalidomide’ lacked face validity.

4.15 The Committee discussed the company’s assumptions around treatment costs in its economic model. Firstly, 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. Secondly, the Committee commented that it would have been 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 company’s incremental cost-effectiveness ratio (ICER) for pomalidomide by about £2000 per quality-adjusted life year (QALY) gained (see section 3.22). Thirdly, the Committee discussed whether it was appropriate for the company to assume that patients who had unused pomalidomide tablets as a result of treatment interruptions
could return them to the NHS. 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 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 appraisal (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 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. The Committee inferred that the higher the utility value for the progressed disease health state, the lower the ICERs estimated by the company’s economic model for pomalidomide compared with each of the 3 comparators. The Committee concluded that because most of the survival gain for pomalidomide was seen in the post-progression phase in the company’s economic model, the company underestimated the ICERs by using a high utility value for progressed disease.
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 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 rather than 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 its equal disutilities for intravenous and subcutaneous therapies were not appropriate.

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 returning tablets from interrupting pomalidomide treatment (see section 4.15) and that corrected the calculation of disutility associated with adverse reactions (see section 3.39). However, the Committee disagreed with the ERG in terms 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 naïve indirect comparison with potentially biased data (see sections 4.8–4.9 and 4.12–4.13). Nevertheless, the Committee noted that the ICERs presented by both the company and the ERG were over £50,000 per QALY gained compared with bortezomib, and that this would further increase when the number of bortezomib cycles was limited to a maximum of 8. The Committee heard from the clinical expert that although there is no standard of care for people with relapsed and refractory multiple myeloma, bendamustine was 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. Moreover, the Committee noted further uncertainty with respect to:

- the company’s model underestimating overall survival in the comparator group (see section 4.12)
- implausible survival benefits in the post-progression phase estimated by the company’s model (see section 4.14)
- the utility value for the progressed disease health state, which may overestimate the QALYs gained for pomalidomide given the disproportionate survival benefits gained in the post-progression phase (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 these uncertainties were accounted for in the economic analysis. The Committee concluded that, even when using the companies approach to establishing the relative effectiveness, the presented
ICERs for pomalidomide that included the Committee’s preferred assumptions were higher than what is normally considered a cost-effective use of NHS resources.

4.19 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. The Committee concluded that these changes in health-related quality-of-life were captured within the company’s economic modelling.

4.20 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.

4.21 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 ranged from 3.9 to 5.3 months based on the Gooding et al. (2013) and Tarant et al. (2013) studies, and 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, 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 agreed that this was a reasonable estimate. The Committee was satisfied that pomalidomide was indicated for a small patient population.

4.22 The Committee considered whether pomalidomide treatment provides an extension to life of at least 3 months compared with current NHS treatment. The Committee highlighted its conclusion that it was not able to judge with any confidence whether pomalidomide is more effective than the current options (see section 4.9), and could therefore not establish the relative effectiveness of pomalidomide and the comparators based on the available evidence. In addition, there was considerable uncertainty
associated with the company’s modelling in that the modelled survival of the comparator group was likely underestimated, and the size of the gains for pomalidomide in the post-progression phase lacked face validity. The Committee was not persuaded that it was presented with estimates of extension to life that were robust, objective or plausible. It concluded that pomalidomide did not fulfil the criteria for being a life-extending, end-of-life treatment. The Committee further concluded that even had pomalidomide fulfilled these criteria, the weight that would have to be placed on the QALYs gained would be too high for pomalidomide to be considered a cost-effective use of NHS resources.

Summary of Appraisal Committee’s key conclusions

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<tr>
<th>TAXXX</th>
<th>Appraisal title:</th>
<th>Section</th>
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<td>Key conclusion</td>
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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.

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.

4.18, 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 multiple treatment options, 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

| Proposed benefits of the technology | 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. | 4.2 |

| How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? |  |  |
| What is the position of the treatment in the pathway of care for the condition? | 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 for fourth-line treatment (including pomalidomide). | 4.3 |
| Adverse reactions | The Committee concluded that, although pomalidomide can lead to several different adverse reactions, it is generally well tolerated. | 4.10 |

### Evidence for clinical effectiveness

<p>| Availability, nature and quality of evidence | 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. The Committee was concerned that the company may have missed relevant evidence for the comparators because of the filters used when searching the literature | 4.5 |
|  |  | 4.8 |</p>
<table>
<thead>
<tr>
<th><strong>Relevance to general clinical practice in the NHS</strong></th>
<th>The Committee understood 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 raised a number of other 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.</th>
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<tr>
<td><strong>Uncertainties generated by the evidence</strong></td>
<td>The Committee was not able to judge with any confidence whether pomalidomide is more effective than the current options. Gooding et al. stated 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 living longer than patients described in both Gooding et al. and Tarant et al., seemed counterintuitive.</td>
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<td>Question</td>
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<td>Evidence for cost effectiveness</td>
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<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>N/A</td>
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<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The Committee concluded that it would have been more appropriate to provide more data to establish the relative effectiveness of pomalidomide. Because of the limitations in the evidence that the company presented, the Committee was not able to judge with any confidence whether pomalidomide is more effective than the current treatment options.</td>
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<td>Availability and nature of evidence</td>
<td>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.</td>
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<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The Committee concluded that it would have preferred the company to use more mature data and to adjust for potential confounders of the association between treatments and survival. The company’s model underestimated the survival of patients in the comparator group. It was not possible to state with any certainty that the comparators were equally effective. The size of the post-progression benefits estimated by the company’s model was implausible. The Committee concluded that because most of the survival gain for pomalidomide was seen post-progression, the company underestimated the ICERs by using a high utility value for progressed disease. The Committee considered that: subcutaneous therapies may be less expensive to administer than intravenous therapies; it would have been more appropriate to limit the number of bortezomib cycles to 8; it was not appropriate to assume that unused pomalidomide tablets from treatment interruptions could be returned to the NHS.</td>
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</tr>
<tr>
<td>Question</td>
<td>Response</td>
<td>Page</td>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The Committee appreciated that the company had included EQ-5D data. The Committee was 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. The Committee concluded that changes in health-related quality-of-life were captured within the company’s economic modelling.</td>
<td>4.16</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>No specific discussion on key drivers because of the uncertainties around, and plausibility of, the assumptions and inputs in the company’s economic model’.</td>
<td>-</td>
</tr>
</tbody>
</table>
Most likely cost-effectiveness estimate (given as an ICER) | For all comparisons, every ICER presented by both the company and the ERG was over £50,000 per QALY gained. The Committee were of the view that the ICERs for pomalidomide would be more likely to increase than to decrease if these uncertainties were accounted for in the economic analysis. | 4.18

### Additional factors taken into account

<table>
<thead>
<tr>
<th>Patient access schemes (PPRS)</th>
<th>N/A</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-of-life considerations</td>
<td>The Committee was not persuaded that the estimates of the extension to life were robust, objective or plausible. It concluded that pomalidomide did not fulfil the criteria for being a life-extending, end-of-life treatment. The Committee further concluded that even had pomalidomide fulfilled these criteria, the weight that would have to be placed on the QALYs would be too high for pomalidomide to be considered a cost-effective use of NHS resources.</td>
<td>4.22</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>Potential equality issues raised during the appraisal were outside the remit of NICE technology appraisal guidance.</td>
<td>-</td>
</tr>
</tbody>
</table>
5  Implementation

5.1 NICE has developed tools to help organisations put this guidance into practice (listed below).

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

6  Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- **Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation** (2014) NICE technology appraisal 311.
- **Bortezomib and thalidomide for the first-line treatment of multiple myeloma** (2011) NICE technology appraisal guidance 228.
- **Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy** (2009) NICE technology appraisal guidance 171.
- **Bortezomib monotherapy for relapsed multiple myeloma** (2007) NICE technology appraisal guidance 129.
Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of NICE technology appraisal guidance 171). NICE technology appraisal. Earliest anticipated date of publication TBC.
- Bortezomib for consolidation therapy after autologous stem cell transplantation for treating multiple myeloma. NICE technology appraisal. Earliest anticipated date of publication February 2015.

NICE pathways

- There is a NICE pathway on ‘blood and bone marrow cancers’, which is available from http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
October 2014
8       Appraisal Committee members, guideline representatives and NICE project team

8.1       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
HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant
Vascular Surgeon, St George's Vascular Institute

Professor Daniel Hochhauser
Consultant in Medical Oncology, UCL 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 (NIHR) Evaluation, Trials and
Studies Coordinating Centre at the University of Southampton
Mr Christopher O'Regan  
Head of Health Technology Assessment & 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

8.2 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
9 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):

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 written evidence to the Committee. They are invited to comment on the ACD.

- Dr Matthew Streetly, Consultant Haematologist, Guys 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