NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation

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

1 Guidance

1.1 Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

2 The technology

2.1 Bortezomib (Velcade, Janssen-Cilag) is an anticancer drug that works by reversible proteasome inhibition. By inhibiting proteasomes (multi-enzyme complexes present in all cells), bortezomib interferes with the cell cycle leading to cell death. It is administered by intravenous infusion or subcutaneous injection. Bortezomib has a UK marketing authorisation for use 'in combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation'.

2.2 The summary of product characteristics lists the following as the most commonly reported adverse reactions for bortezomib: nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of bortezomib is £762 per 3.5-mg vial (excluding VAT; British National Formulary [BNF] edition 66. According to the marketing authorisation bortezomib should be given in combination with dexamethasone (4 cycles of 21 days each) or with dexamethasone and thalidomide (4 cycles of 28 days each; 2 additional cycles of 28 days each for patients with at least partial response after the fourth cycle). Four intravenous infusions or subcutaneous injections of bortezomib are administered per cycle, on days 1, 4, 8 and 11 of each cycle. The average cost of a course of treatment with bortezomib given with dexamethasone is estimated to be £12,261 and the average cost of a course of treatment with bortezomib given with dexamethasone and thalidomide is estimated to be £24,840. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of bortezomib and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The main clinical evidence submitted by the manufacturer for the bortezomib, thalidomide and dexamethasone regimen came from the PETHEMA trial in which in people with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplantation received up to 6 cycles of bortezomib, thalidomide and dexamethasone, or thalidomide and dexamethasone. The evidence for the bortezomib and dexamethasone regimen came from the IFM trial, which compared 4 cycles of bortezomib and dexamethasone with 4 cycles of vincristine, doxorubicin and dexamethasone. The manufacturer also submitted data from the GIMEMA trial which compared the efficacy and safety of 3 cycles of bortezomib, thalidomide and dexamethasone with 3 cycles of thalidomide and dexamethasone as induction treatment before autologous stem cell transplantation followed by consolidation treatment with 2 cycles of either bortezomib, thalidomide and dexamethasone or thalidomide and dexamethasone. However, the manufacturer highlighted that the PETHEMA trial study design better reflected how the bortezomib, thalidomide and dexamethasone regimen is expected to be used in the UK and therefore was the focus of the manufacturer's submission. Data from the HOVON trial were provided by the manufacturer, but the bortezomib-containing regimen included in this study, bortezomib, doxorubicin and dexamethasone, was not approved by the European Medicines Agency and is therefore not a licensed regimen.

3.2 The PETHEMA trial was a randomised, open-label phase III study that compared the efficacy and safety of bortezomib in combination with thalidomide and dexamethasone against thalidomide and dexamethasone in people with newly diagnosed symptomatic multiple myeloma and measurable disease (serum and/or urine M protein), who were eligible for autologous stem cell transplantation.

Patients were randomised to either bortezomib, thalidomide and dexamethasone (n=130) or thalidomide and dexamethasone (n=127), both of which consisted of 6 cycles of 28 days, with each cycle including 4 infusions of bortezomib, oral dexamethasone (40 mg on days 1–4 and 8–11 of each cycle) and oral thalidomide (50 mg daily). After transplantation, patients who continued in the trial were re-randomised to receive 1 of 3 maintenance treatments (interferon alfa-2b, thalidomide, or bortezomib plus thalidomide). Maintenance therapy was continued for up to 3 years, or until disease progression. Although the PETHEMA trial did not incorporate the discontinuation rule as per the summary of product characteristics, because patients in the GIMEMA trial received only 3 cycles, the manufacturer stated that the PETHEMA trial design better reflected how the bortezomib, thalidomide and dexamethasone regimen is expected to be used in the UK.

3.3 The GIMEMA trial was a randomised, open-label, phase III study in 480 patients with newly diagnosed, previously untreated symptomatic multiple myeloma with measurable disease. The study was designed to compare the efficacy and safety of 3 cycles of bortezomib, thalidomide and dexamethasone with 3 cycles of thalidomide and dexamethasone as induction treatment before autologous stem cell transplantation. It also evaluated subsequent consolidation treatment consisting of 2 cycles of either bortezomib, thalidomide and dexamethasone, or thalidomide and dexamethasone. Maintenance treatment with dexamethasone was continued until disease progression or relapse. Each cycle of induction therapy consisted of 1.3 mg/m^2 of bortezomib on days 1, 4, 8 and 11, with 100 mg of thalidomide daily for the first 14 days and 200 mg thereafter. Dexamethasone 40 mg was administered on days 1, 2, 4, 5, 8, 9, 11 and 12. Instead of the dosage recommended in the summary of product characteristics, patients

randomised to the bortezomib, thalidomide and dexamethasone induction group received only 3 cycles of bortezomib-based treatment.

3.4 The IFM trial was a randomised, open-label study designed to compare the efficacy and safety of bortezomib and dexamethasone (with or without consolidation treatment with dexamethasone, cyclophosphamide, etoposide and cis-platinum) against vincristine, doxorubicin and dexamethasone (with or without intensification). Treatment with bortezomib and dexamethasone consisted of 4 21-day cycles of 1.3 mg/m^2 of bortezomib and 40 mg of dexamethasone. However, the manufacturer stated that only the results without the intensification step were relevant to the decision problem. Moreover, as discussed previously, the manufacturer stated that this comparison was not in line with the decision problem because the vincristine, doxorubicin and dexamethasone regimen is not a thalidomide-containing regimen and therefore not an appropriate comparator. The manufacturer also stated that the vincristine, doxorubicin and dexamethasone regimen is not routinely used in UK clinical practice and excluded this from its base-case analysis.

3.5 The primary outcome measures in the PETHEMA, GIMEMA and IFM trials were response rates reported after induction and after transplant. The manufacturer's submission reported 'response' in terms of:

- complete response
- near-complete response
- very good partial response (not used in the PETHEMA trial)
- partial response
- progressive disease
- overall response rate.

Overall response rate was calculated as the total proportion of patients who had a partial response or better. All response rates were evaluated using the European Group of Blood and Bone Marrow Transplant (EBMT) criteria and the International Myeloma Working Group uniform criteria.

3.6 Patients who received bortezomib (bortezomib, thalidomide and dexamethasone) had a statistically significant difference in overall response rate after induction compared with the thalidomide regimen (thalidomide and dexamethasone) in both the PETHEMA (84.6% compared with 61.4%, $p<0.001$) and GIMEMA (93.2% compared with 78.6%, $p<0.0001$) trials. This difference in treatment effect on overall response rate was maintained after transplant (77.7% compared with 56.7%, $p<0.001$ in the PETHEMA trial and 93.2% compared with 84.5%, $p<0.0025$ in the GIMEMA trial). Patients receiving bortezomib in PETHEMA and GIMEMA also showed statistically higher post-induction and post-transplant complete response rates than those on the thalidomide-containing regimen. In the PETHEMA trial, 35.4% in the bortezomib, thalidomide and dexamethasone treatment group had a post-induction complete response compared with 13.4% in the thalidomide and dexamethasone group ($p<0.001$). In the GIMEMA trial, 18.6% had a post-induction complete response in the bortezomib, thalidomide and dexamethasone treatment group compared with 4.6% in the thalidomide and dexamethasone group ($p<0.0001$). In the post-transplant period, statistically significant differences were maintained for the bortezomib, thalidomide and dexamethasone treatment groups in both the PETHEMA and GIMEMA trials ($p<0.001$ and $p=0.0004$ respectively). Both the PETHEMA and GIMEMA trials reported a statistically significant lower proportion of patients experiencing disease progression when treated with bortezomib, thalidomide and dexamethasone

compared with patients treated with thalidomide and dexamethasone induction therapy in the post-induction period (6.2% and 23.6%, p=0.0004 in the PETHEMA trial; and 0% and 5.0%, p<0.0005 in the GIMEMA trial).

3.7 In the IFM trial, people who received bortezomib in combination with dexamethasone showed a statistically significant difference in overall response rate after induction compared with vincristine, doxorubicin and dexamethasone (77.1% compared with 60.7%, p<0.001) but this difference was not maintained after stem cell transplantation (79.6% compared with 74.4%, p=0.179).

3.8 Secondary outcomes reported in the PETHEMA, GIMEMA, IFM and MRC Myeloma IX (described in section 3.12) trials included:

- progression-free survival
- time to progression
- overall survival
- proportion of patients who had stem cell transplantation
- adverse events.

Progression-free survival was measured from the date of randomisation to the date of disease progression or death from any cause, whichever occurred first. Time to progression was calculated from the date of randomisation to the date of disease progression or death due to disease progression. Overall survival was calculated from the date of randomisation to the date of death from any cause for the intention-to-treat populations. The manufacturer reported the unadjusted hazard ratios for progression-free survival for the PETHEMA, GIMEMA and IFM trials. Median follow-up in the trials was 35.9 months (PETHEMA), 36 months (GIMEMA) and 33 months (IFM). Progression-free survival was longer in the bortezomib, thalidomide and

dexamethasone arms of both the PETHEMA and GIMEMA trials than the thalidomide and dexamethasone arms, and the difference was statistically significant (PETHEMA hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.45 to 0.92, p=0.015; GIMEMA HR 0.63, 95% CI 0.45 to 0.88, p=0.0061). Progression-free survival was longer in the bortezomib and dexamethasone arm of the IFM trial compared with the vincristine, doxorubicin and dexamethasone arm, but the difference was not statistically significant (IFM HR 0.88, 95% CI 0.70 to 1.11, p value not reported).

3.9 The manufacturer's submission reported the median time to progression and time to progression hazard ratios from the PETHEMA and IFM trials. In the PETHEMA study there was a statistically significant lower hazard of progression in patients treated with bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone (HR 0.64, 95% CI 0.44 to 0.93, p=0.017). No statistically significant difference in median time to progression was reported. In the IFM study there was a numerically lower hazard of progression in patients treated with bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone but this was not statistically significant (HR 0.82, 95% CI 0.63 to 1.06, p value no reported).

3.10 The manufacturer's submission reported unadjusted overall survival hazard ratios for the PETHEMA and IFM trials. Median overall survival was not reached in either the PETHEMA trial (bortezomib, thalidomide and dexamethasone compared against thalidomide and dexamethasone, hazard ratio 0.80, 95% CI 0.48 to 1.34, p=0.393) or IFM trial (bortezomib and dexamethasone compared against vincristine, doxorubicin and dexamethasone, HR 0.8, 95% CI 0.54 to 1.19; p value not reported) and there was no statistically significant difference in overall survival between the

treatment arms in each study. The manufacturer's submission highlighted clinical specialist opinion that the durations of the trials were too short to allow differences in overall survival and progression-free survival between treatment groups to be sufficiently captured, given the relatively long survival in this patient population after an autologous stem cell transplant.

3.11 The bortezomib-containing arms of the PETHEMA and GIMEMA trials (bortezomib, thalidomide and dexamethasone) reported higher proportions of patients having stem cell transplantation compared with the thalidomide and dexamethasone arms (80.8% compared with 61.4% in PETHEMA, and 88.0% compared with 82% in GIMEMA). In addition, the bortezomib and dexamethasone arm of the IFM trial reported higher proportions of patients having stem cell transplantation compared with the vincristine, doxorubicin and dexamethasone arm (89.1% compared with 81.8%). However, no statistical tests were reported.

3.12 In the absence of head-to-head trials comparing bortezomib-based regimens against cyclophosphamide in combination with thalidomide and dexamethasone, the manufacturer originally presented an indirect comparison based on the PETHEMA, GIMEMA, HOVON, IFM and MRC Myeloma IX randomised controlled trials. The MRC Myeloma IX trial is the only trial that has compared the efficacy of cyclophosphamide, vincristine, doxorubicin and dexamethasone against cyclophosphamide, thalidomide and dexamethasone in 1111 patients with newly diagnosed symptomatic myeloma. In this trial, patients were randomised to receive induction chemotherapy following either an intensive or non-intensive (attenuated treatment) pathway. The manufacturer considered that the MRC Myeloma IX trial provided the only potential evidence that allowed any form of comparison to

be made between bortezomib-based regimens and cyclophosphamide, thalidomide and dexamethasone. The bortezomib plus doxorubicin and dexamethasone regimen (used in the HOVON trial) was included as part of the evidence submission but the manufacturer considered its inclusion in the indirect comparison to be inappropriate because this regimen was not included in the marketing authorisation. The manufacturer stated that a network could not be formed between the available trials, and an indirect comparison with cyclophosphamide, thalidomide and dexamethasone was not possible. In addition, bortezomib and dexamethasone could not be linked to a thalidomide-containing regimen. The manufacturer highlighted that assumptions to overcome the network limitations would generate considerable uncertainties and unreliable results. The manufacturer stated that an incremental analysis of the 2 licensed bortezomib regimens was therefore also not possible and stated that the base case should focus on the comparison of bortezomib, thalidomide and dexamethasone with thalidomide and dexamethasone.

3.13 The manufacturer presented a summary of results for adverse events for the PETHEMA, GIMEMA, IFM and MRC Myeloma IX trials. Only adverse events for the post-induction phase were reported because the manufacturer considered the adverse events for the post-transplant phase not to be relevant. Across all trials a similar proportion of patients reported any adverse event, grade 3/4 adverse events, and serious adverse events in both the bortezomib and comparator treatment arms. However, in the PETHEMA trial a statistically significantly greater number of total treatment-related adverse events was reported during induction with bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone (relative risk [RR]=1.42; 95% CI 1.17 to 1.73). In the GIMEMA trial a statistically significantly greater proportion of

patients receiving bortezomib, thalidomide and dexamethasone experienced any grade 3/4 adverse event than those receiving thalidomide and dexamethasone (RR=1.69; 95% CI 1.36 to 2.08). The 2 most common treatment-related adverse events in the PETHEMA trial (pneumonia and peripheral neuropathy) occurred more frequently in the bortezomib, thalidomide and dexamethasone arm than in the thalidomide and dexamethasone arm. The manufacturer's submission highlights that in the 4 bortezomib-based studies, bortezomib was given intravenously. In terms of tolerability, total withdrawals and withdrawals due to disease progression were statistically significantly less in the bortezomib, thalidomide and dexamethasone arm than the thalidomide and dexamethasone arm in the PETHEMA trial (HR 0.51 [95% CI 0.34 to 0.77] and HR 0.45 [95% CI 0.25 to 0.84] respectively).

3.14 No health-related quality of life data were collected in the trials of bortezomib-containing regimens. To inform the cost-effectiveness evidence, the manufacturer conducted a systematic literature search to identify publications relevant to the decision problem in relation to health-related quality of life.

Evidence Review Group comments

3.15 The ERG stated that the manufacturer's search strategy was clear and comprehensive. The ERG noted that 5 trials were included in the manufacturer's original submission, but highlighted that only 2 trials (PETHEMA and GIMEMA) met the NICE scope and focused its critique on these trials. This was in line with the manufacturer's addendum. The ERG stated that both trials were unblinded and therefore at risk of detection bias. The ERG agreed with the manufacturer that the baseline characteristics were generally similar across the trials. However, the ERG also highlighted that the

PETHEMA and GIMEMA trials excluded patients older than 65 years, which does not reflect UK clinical practice.

3.16 The ERG commented that overall, the manufacturer's approach to the trial statistics was appropriate and reasonably well reported. However, the ERG commented that long-term outcomes such as progression-free survival and overall survival may be confounded by post-induction consolidation and maintenance treatments that do not reflect current UK clinical practice. The ERG also noted that there is uncertainty in the robustness of the progression-free survival and overall survival results because of the high censoring of data in the bortezomib, thalidomide and dexamethasone, and thalidomide and dexamethasone arms of the PETHEMA trial (57.7% and 44.9% respectively in the progression-free survival analysis, and 80.0% and 74.8% respectively in the overall survival analysis).

3.17 The ERG noted that the manufacturer had highlighted that the results from the indirect comparison were subject to substantial uncertainty and were therefore not included in the economic modelling. The ERG agreed with this approach.

Cost effectiveness

3.18 The manufacturer conducted a systematic search of the literature and identified 3 cost-effectiveness studies relevant to the decision problem. The manufacturer conducted a quality assessment of these studies but did not discuss them further in the submission.

3.19 The manufacturer developed an Excel-based economic model to assess the cost effectiveness of bortezomib-based induction regimens compared with thalidomide-based induction regimens. As discussed previously, the manufacturer's base-case analysis

focused on the cost-effectiveness analysis of bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The manufacturer presented cost-effectiveness analyses of bortezomib, thalidomide and dexamethasone (including the discontinuation rule stipulated in the marketing authorisation submitted as an addendum submission) compared with thalidomide and dexamethasone, and of bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone. The manufacturer acknowledged that the comparison with vincristine, doxorubicin and dexamethasone did not reflect current best clinical practice in the UK. The manufacturer stated that no comparisons of the bortezomib and dexamethasone regimen with relevant thalidomide-containing regimens (such as cyclophosphamide, thalidomide and dexamethasone) were possible using indirect mixed treatment comparisons.

3.20 The manufacturer chose a state-transition Markov model, with a cycle length of 1 month, to reflect the length of a course of treatment with bortezomib, thalidomide and dexamethasone (28 days) and because clinical outcomes are reported in months. The model did not include a half-cycle correction because the cycle length was short relative to the time horizon used in the model. Costs and quality-adjusted life years (QALYs) were discounted over a lifetime (30 years) time horizon at 3.5% per annum. The manufacturer stated that the model captured the 2 most important outcomes: post-induction response rate and overall survival. However, the manufacturer clarified that because the pivotal trials were not powered to detect a statistically significant difference in overall survival, the model was based on response rate, and the relationship between response rate and overall survival was quantified using long-term survival data from older trials in the same patient population. The model assumed that patients entered

at the start of their induction therapy. After induction, patients in the model entered one of 3 health states: complete response, partial response, or non-responders (defined as minimal response, stable disease and progressive disease respectively). Depending on their post-induction response rate, patients subsequently proceeded to high-dose chemotherapy and stem cell transplantation or to the post-induction progression-free survival health state (non-stem cell transplant group). After induction, all patients were assumed to incur the same survival benefit, which was dependent only on their response rate after the induction phase and was independent of the actual induction regimen that they received. On disease progression, patients would then receive a second treatment, followed by third-line and subsequent lines of treatment after further progression.

3.21 Post-induction response rates were used as the main measure of efficacy in the model. Stem cell transplant rates for each response category in each treatment arm were used in the model evaluating bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The economic model for bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone used total stem cell transplant rates rather than transplant rates for each response category. The model also included mortality during the induction and transplant periods.

3.22 In order to model long-term survival based on the post-induction response rates, the manufacturer extracted overall survival data from the MRC Myeloma VII trial because overall survival data from the PETHEMA trial were considered immature. The MRC Myeloma VII trial randomised a total of 407 previously untreated multiple myeloma patients to conventional chemotherapy (n=200) or high-

dose chemotherapy followed by autologous stem cell transplant (n=201). The 5-year survival in the high-dose chemotherapy followed by autologous stem cell transplant group was 88.6 months (95% CI 61.4, upper CI not reported) for patients who had a complete response, 39.8 months (95% CI 33.8 to 61.4) for patients who had a partial response, and 25.6 months (95% CI 7.0 to 31.3) for patients who had no response. For a scenario analysis, the manufacturer also used long-term survival data from the IFM90 trial from 1996.

3.23 The manufacturer used post-transplant time to progression from the PETHEMA trial to determine the probabilities of transition from the post-transplant progression-free health state to the start of second-line therapies. The manufacturer assumed that time to progression is affected by the interventions because it was modelled using separate parametric curves by treatment and response category. In the base case, time-to-progression transition probabilities were derived from exponential curves fitted to the PETHEMA data. Constant transition probabilities were used for transition from the second-line to the third-line health state across the 2 interventions, the estimates for which were derived from the subgroups of patients who had 1 or 2 lines of treatment respectively in the APEX trial (which compared bortezomib monotherapy with high-dose dexamethasone in patients with relapsed multiple myeloma). Probabilities of transition from third to further lines of treatment were derived by applying an exponential distribution to the time-to-progression data from the APEX trial. The overall survival data from the MRC Myeloma VII trial were used to determine the length of time that patients remained in the further lines of treatment health state before moving to the death state.

3.24 The manufacturer conducted a systematic search of the literature to identify publications that identified health-related quality of life data relevant to the decision problem. Five relevant studies were identified, of which 3 reflected the current UK patient population and clinical practice. The manufacturer selected the van Agthoven study as the base-case source of utility values because the utility values were obtained using EQ-5D. The study by van Agthoven et al. compared chemotherapy (n=129) with intensive chemotherapy followed by myeloablative chemotherapy with stem cell transplantation (n=132) and total body irradiation treatment regimens. Patients were from the Netherlands and Belgium, under the age of 65 years, and had newly diagnosed and untreated multiple myeloma. They received 3 or 4 cycles of vincristine, doxorubicin and dexamethasone and 2 cycles of intermediate-dose melphalan, after which they were randomised to have either stem cell transplantation and interferon maintenance, or interferon maintenance only. The manufacturer applied a disutility of 0.02 to each patient experiencing an adverse event associated with induction therapy.

3.25 The costs applied in the model were taken from the BNF edition 64 (2012) and the 2012–13 Chemotherapy Regimens List. Administration of chemotherapy drugs, outpatient visits and tests as part of disease and treatment monitoring and the costs relating to stem cell transplantation were taken from the 2011–12 National Schedule Reference costs. The costs associated with treating adverse events were based on inpatient, outpatient or day-case visit National Schedule Reference costs. The manufacturer presented unit costs associated with each of the first-line induction therapies as well as drugs for prophylaxis, administration and monitoring. The total cost, including prophylaxis, administration and monitoring, of the bortezomib, thalidomide and dexamethasone

regimen was £28,034, which compared with a total cost of £8,865 for thalidomide and dexamethasone. The total cost of the bortezomib and dexamethasone regimen was £14,104, whereas the total cost of vincristine, doxorubicin and dexamethasone was £2732.

3.26 The manufacturer's economic model estimated a difference in total costs between the bortezomib, thalidomide and dexamethasone and the thalidomide and dexamethasone regimens of £20,682. The bortezomib, thalidomide and dexamethasone regimen was associated with a 1.01 QALY gain compared with thalidomide and dexamethasone. The manufacturer's estimated base-case incremental cost-effectiveness ratio (ICER) for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone was £20,468 per QALY gained. The incremental cost difference between the bortezomib and dexamethasone and the vincristine, doxorubicin and dexamethasone regimens was £12,710, and bortezomib and dexamethasone was associated with an incremental QALY gain of 0.88 resulting in an estimated ICER of £14,446 per QALY gained for the bortezomib and dexamethasone regimen compared with vincristine, doxorubicin and dexamethasone.

3.27 The manufacturer's deterministic sensitivity analyses highlighted that the results for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone were most sensitive to the mortality for patients who had a complete response after induction therapy, and to drug costs. If the complete response mortality rate was varied within its 95% confidence interval, other things being equal, the ICER ranged from £17,018 to £28,867 per QALY gained. For the bortezomib, thalidomide and dexamethasone drug costs, sensitivity analyses were conducted using 4, 5 and 6

cycles of induction therapies. This was based on clinical opinion that the number of cycles will vary from one patient to another. The ICER range for the sensitivity analysis varying bortezomib, thalidomide and dexamethasone drug costs was £15,761 to £25,662 per QALY gained. For all other parameters varied in the sensitivity analyses, the ICER remained between £16,000 and £25,000 per QALY gained. Deterministic sensitivity analyses were also presented by the manufacturer for the comparison between the bortezomib and dexamethasone, and the vincristine, doxorubicin and dexamethasone regimens. Here, the results were most sensitive to the mortality for patients with complete response after induction therapy, with ICERs ranging from £10,961 to £18,354 per QALY gained.

3.28 The results of the manufacturer's probabilistic sensitivity analysis showed that, at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained, there was a 35.4% and 71.3% probability respectively of the bortezomib, thalidomide and dexamethasone regimen being cost effective when compared with thalidomide and dexamethasone. The manufacturer estimated that at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained, there was a 68.9% and 83.2% probability respectively of the bortezomib and dexamethasone regimen being cost effective compared with vincristine, doxorubicin and dexamethasone.

3.29 The ERG stated that the structure of the model was consistent with the clinical pathway of care for multiple myeloma and was clearly presented. However, the ERG highlighted that the manufacturer's analysis of bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone was outside the scope. It also highlighted that, given that the comparator in routine use in UK clinical practice is the cyclophosphamide, thalidomide and

dexamethasone regimen, the comparison of bortezomib, thalidomide and dexamethasone with thalidomide and dexamethasone was not entirely relevant to clinical practice.

3.30 The ERG also expressed some concerns that the model extrapolated level of response after induction therapy to long-term survival and time to progression based on data from the MRC Myeloma VII trial. The ERG cautioned that the MRC Myeloma VII trial was old and its outcomes may not reflect the more advanced treatments available today. Moreover, the ERG stated that data from the MRC Myeloma VII trial related to maximal response to treatment rather than post-induction response rate, and the resulting survival curves might be confounded to some extent with post-stem cell transplant response. The ERG clinical expert agreed that response rate at induction predicts progression-free survival and overall survival. However, the ERG stated that other surrogate outcomes, such as post-stem cell transplant response rate, may offer a better prediction of progression-free survival and overall survival. The ERG observed that although the model had separate states for those who received a stem cell transplant and those who did not, the model attached no explicit survival benefit to a stem cell transplant other than that achieved by delaying the transition to the post-induction/post-transplant progression-free survival state for the duration of the stem cell transplant period. The ERG clinical expert stated that stem cell transplantation offers a survival benefit of 12–18 months compared with no transplant, and the ERG stated that it would have been more transparent to distinguish the separate effects on survival of post-induction response and stem cell transplantation. Alternatively, post-stem cell transplant response rate could have been considered because it has been shown to be statistically significantly associated with improved overall survival. Overall, the ERG stated that external validity would have been

strengthened if the model had been based on overall survival and time to progression Kaplan–Meier curves or post-stem cell transplant response, rather than post-induction response. The ERG was concerned that in the absence of this the results were systematically biased in favour of bortezomib, thalidomide and dexamethasone.

3.31 The ERG stated that, in contrast to the manufacturer's description in the submission, the model implicitly assumed a continuing effect of induction treatment after induction is complete, because separate time to progression curves were used for each induction treatment arm and stem cell transplant mortality was also applied separately by treatment arm. The ERG also highlighted that, contrary to statements in the manufacturer's submission, the probability of receiving a stem cell transplant was not dependent on post-induction response, but only on treatment received.

3.32 The ERG noted the manufacturer's approach to calculating transition probabilities (section 3.23), and stated that the exponential distribution fitted to the PETHEMA complete response time to progression data for bortezomib, thalidomide and dexamethasone resulted in a shorter median survival time (approximately 61 months) than the exponential distribution fitted to complete response time to progression data for patients receiving thalidomide and dexamethasone (median survival approximately 98 months). The ERG stated that this contrasted with overall findings for progression-free survival in the trial publication in which median progression-free survival was statistically significantly higher with bortezomib, thalidomide and dexamethasone than with thalidomide and dexamethasone. The ERG noted that the manufacturer derived transition probabilities for third and further treatment lines using data from the APEX trial, which compared bortezomib monotherapy

with high-dose dexamethasone in patients with relapsed multiple myeloma. The ERG commented that because the APEX trial used bortezomib as a monotherapy treatment, it may have had different survival outcomes to those seen with bortezomib combination therapy.

3.33 The ERG considered that the costs included in the model were reasonable. However, the ERG identified that a number of changes to the manufacturer's addendum economic model, submitted to take account of the discontinuation rule stipulated for bortezomib, thalidomide and dexamethasone (see section 3.19), were not documented by the manufacturer. Although the manufacturer's addendum referred to the original submission for discussion of resource identification, measurement and valuation, the ERG noted that many of the costs in the revised model were different from those in the original model. These included costs for drugs, induction, stem cell transplant, second-line treatment, third-line treatment, and some monitoring costs. The ERG noted that although these changes were generally minor, some were substantial. For example, the administration costs for high-dose dexamethasone increased from £168 to £1242 in second-line therapy, and from £168 to £1288 in third-line therapy. The ERG stated that when considering only model changes and assumptions that were documented in the manufacturer's addendum, the ICER was £23,958 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, compared with the £20,468 per QALY gained reported in the manufacturer's addendum.

3.34 The ERG conducted a series of additional exploratory analyses. It considered that the MRC Myeloma VII trial was old and its outcomes may not reflect the more advanced treatments available

today (see section 3.30) and noted that the manufacturer's sensitivity analysis used an even older study (the IFM90). Therefore, the ERG obtained data from a study by Alvares and from the NMSG 5/94 study to conduct scenario analyses. The NMSG 5/94 study was a prospective study with 247 patients recruited between 1994 and 1997, and Alvares was a retrospective study with 383 patients in England diagnosed with multiple myeloma between 1985 and 2004. The ERG considered that the Alvares data provided the better fit to the PETHEMA overall survival data. The ERG commented that because median overall survival for partial and non-responders in the Alvares study was much better than in the MRC Myeloma VII trial, this resulted in an increase in the base-case ICER from £20,468 per QALY gained to £30,368 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The ERG also provided the ICER using the data from the NMSG 5/94 study, but this did not include the discontinuation rule for the bortezomib, thalidomide and dexamethasone regimen and is therefore not presented. However, it resulted in a higher ICER than using the Alvares study data. The ERG also highlighted that data from the MRC Myeloma VII trial related to maximal response to treatment rather than post-induction response rate and that this was arguably more similar to post-stem cell transplant response. The ERG commented that post-stem cell transplant response rates provided a more consistent fit to the MRC Myeloma VII data and would better predict overall survival. Applying post-stem cell transplant response rates alone increased the manufacturer's base-case ICER from £20,468 to £26,292 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The ERG combined its preferred scenario analyses, that is, using data from Alvares to inform long-

term survival and using post-stem cell transplant response rates. This resulted in an ICER of £38,985 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone.

3.35 The ERG conducted further exploratory analyses using the relevant economic model outputs from the manufacturer's base-case cost-effectiveness results to calculate ICERs for all treatments compared with thalidomide and dexamethasone and with cyclophosphamide, thalidomide and dexamethasone, the latter of which is a more relevant comparator regimen in a UK population. The ERG commented that all results should be treated with extreme caution as they compare individual arms of separate trials, without adjusting for trial populations. Furthermore there were differences in the trial designs. For these reasons, the results should not be directly compared. Using the manufacturer's base-case model to compare bortezomib, thalidomide and dexamethasone against cyclophosphamide, thalidomide and dexamethasone resulted in an exploratory ICER of £228,159 per QALY gained. The ERG then applied its preferred assumptions, that is, using data from Alvares to inform long-term survival and using post-stem cell transplant response rates. This resulted in an exploratory ICER for bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone of £81,983 per QALY gained. The ERG conducted the same exploratory analyses in order to calculate ICERs for the bortezomib and dexamethasone regimen compared with thalidomide and dexamethasone and with cyclophosphamide, thalidomide and dexamethasone. The ERG applied data from Alvares and used post-stem cell transplant response rates, and this resulted in an ICER of £26,701 per QALY gained for bortezomib and dexamethasone compared with thalidomide and

dexamethasone. However, bortezomib and dexamethasone was dominated by (that is, was less effective and more expensive than) cyclophosphamide, thalidomide and dexamethasone.

Manufacturer's response to the appraisal consultation document

3.36 Additional analyses were provided by the manufacturer in response to NICE's request for further work on the comparison between the regimen containing bortezomib and dexamethasone compared with the most relevant comparator (cyclophosphamide, thalidomide and dexamethasone) or an alternative comparator in circumstances when cyclophosphamide, thalidomide and dexamethasone is not suitable. Although the Committee did not request further analyses relating to the bortezomib, thalidomide and dexamethasone regimen, the manufacturer provided an amended model containing some revised assumptions to reflect some of the concerns raised by the ERG and the Committee's considerations in the appraisal consultation document.

3.37 The manufacturer acknowledged that the cyclophosphamide, thalidomide and dexamethasone regimen was the most relevant comparator in UK clinical practice. However, it did not provide a comparison for the bortezomib, thalidomide and dexamethasone regimen with the cyclophosphamide, thalidomide and dexamethasone regimen. It highlighted that for the comparison of the bortezomib, thalidomide and dexamethasone regimen with the thalidomide and dexamethasone regimen presented in the manufacturer's base-case analysis, it was important to evaluate how much additional benefit would be gained in terms of response rates if cyclophosphamide was to be added to thalidomide and dexamethasone. The manufacturer stated that threshold analyses

performed in its original submission indicated that the complete response rate for cyclophosphamide, thalidomide and dexamethasone would have to be nearly double that observed in the PETHEMA trial for thalidomide and dexamethasone for the ICER for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone to reach £30,000 per QALY gained. Therefore the manufacturer stated that the incremental clinical efficacy of cyclophosphamide, thalidomide and dexamethasone would not be substantially greater than thalidomide and dexamethasone.

3.38 The manufacturer updated all the economic models so that:

- a survival benefit of 11.8 months for people who received a stem cell transplant was explicitly captured
- post-induction rates were applied on an intention-to-treat basis to all patients in the model
- probabilities of receiving a stem cell transplant were applied only to those who received a transplant
- transition probabilities to second-line therapy were included by treatment arm (rather than by treatment arm and response rate)
- drug administration costs were updated assuming that bortezomib is subcutaneously administered.

3.39 For the model comparing the bortezomib, thalidomide and dexamethasone regimen against thalidomide and dexamethasone, the manufacturer provided a revised base-case ICER of £17,841 per QALY gained. Sensitivity analyses using data from alternative sources to inform overall survival were presented; using long-term overall survival data from the Alvares and NMSG 5/94 studies resulted in ICERs of £22,696 and £39,618 per QALY gained respectively. The probabilistic ICER for the manufacturer's revised

base-case was £22,289 per QALY gained. The probabilistic ICERs for the sensitivity analyses using Alvares and NSMG5/94 were £22,952 and £39,881 per QALY gained respectively. The manufacturer also carried out sensitivity analyses by fitting parametric curves (exponential, Weibull and log-logistics) to the PETHEMA Kaplan-Meier curves. It selected the parametric functions it thought were most appropriate, providing justification for their suitability based on face validity with the trial data, resulting in a deterministic ICER of £19,359 per QALY gained and a probabilistic ICER of £19,668 per QALY gained. The manufacturer maintained that the most appropriate source to inform overall survival in model was from the MRC Myeloma VII trial.

3.40 For the indirect comparison of bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone, the manufacturer used a 'matching-adjusted indirect comparison' method to account for differences in patients' baseline characteristics between the available trials. This created a new set of post-induction response rates, stem cell transplant rates and the post-transplant response rates for the bortezomib and dexamethasone arm. Using the MRC Myeloma VII trial as the source for long-term survival, the manufacturer's base-case deterministic ICER for the comparison of bortezomib and dexamethasone against cyclophosphamide, thalidomide and dexamethasone was £20,588 per QALY gained. The probabilistic ICER was £22,305 per QALY gained. Using long-term survival data from Alvares and NMSG 5/94 resulted in deterministic ICERs of £24,267 and £33,435 per QALY gained respectively, and the corresponding probabilistic ICERs were £23,816 and £33,107 per QALY gained. The manufacturer presented sensitivity by fitting parametric curves (exponential, Weibull and log-logistics) to the PETHEMA Kaplan-Meier curves (see section 3.39) which resulted

in a deterministic ICER of £18,864 per QALY gained and a probabilistic ICER of £19,057 per QALY gained.

3.41 In response to the Committee's request for a comparison of bortezomib and dexamethasone with a relevant comparator when cyclophosphamide, thalidomide and dexamethasone is not suitable, the manufacturer highlighted that the only relevant comparator for which there was direct available evidence was vincristine, doxorubicin and dexamethasone, which might be assumed to be approximately equivalent to cyclophosphamide and dexamethasone or other options lacking thalidomide. Therefore, the manufacturer presented a deterministic base-case ICER for bortezomib and dexamethasone compared with vincristine, thalidomide and dexamethasone (including the model amendments highlighted in section 3.38) of £18,914 per QALY gained, and a probabilistic ICER of £20,096 per QALY gained. Sensitivity analyses were presented for the alternative sources of overall survival using data from the Alvares and NMSG 5/94 studies and fitting parametric curves to the PETHEMA data, which resulted in deterministic ICERs of £25,575, £42,811 and £18,489 per QALY gained respectively. The corresponding probabilistic ICERs were £25,494, £42,528 and £18,761 per QALY gained.

3.42 The ERG noted that the model structure had changed substantially from the original models and that the new approach appeared to be more intuitive. However, it highlighted that the manufacturer had not checked the external validity by validating overall survival against the PETHEMA trial.

3.43 The ERG noted that the manufacturer's analysis of bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, using the MRC Myeloma VII as the source of overall survival, provided a poor fit for overall survival compared

with the observed data in the PETHEMA trial. It stated that the model consistently underestimated overall survival and was systematically biased in favour of the bortezomib, thalidomide and dexamethasone regimen. The ERG noted that the bias appeared even more pronounced in the new analyses. The ERG maintained that the sensitivity analyses using data from the Alvares or NMSG 5/94 trials was a better fit for overall survival than the base-case analysis (using long-term overall survival data from the MRC Myeloma VII trial).

3.44 For the comparison of the bortezomib and dexamethasone regimen with the cyclophosphamide, thalidomide and dexamethasone regimen, the ERG noted that stem cell transplant rates used in the manufacturer's model were 89.1% for the bortezomib arm (taken from the IFM trial) and 66.7% for the cyclophosphamide arm (taken from the MRC Myeloma IX trial). The ERG commented that the stem cell transplant rate for the cyclophosphamide-containing arm was inconsistent with the response data and may have substantially biased the bortezomib and dexamethasone cohort. The ERG explored the impact of assuming that the stem cell transplant rates for the cyclophosphamide-containing arm were similar to the IFM comparator arm (that is, 81.8% for vincristine, doxorubicin and dexamethasone) to better reflect the smaller differences observed between treatment arms in the other bortezomib trials (GIMEMA, HOVON and IFM). This increased the manufacturer's base-case ICER from £20,588 to £36,712 per QALY gained.

3.45 The ERG stated that the manufacturer's analysis of bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone provided a poor fit for overall survival compared with the observed data in the IFM trial. The ERG noted that the

manufacturer provided sensitivity analyses using alternative data sources and parametric curves to model overall survival and that it considered that these sensitivity analyses, using the Alvares or NMSG 5/94 trials, were a better fit for overall survival than the base-case analysis (using long term overall survival data from the MRC Myeloma VII trial).

3.46 Full details of all the evidence are in the manufacturer's submission and the ERG report. Further evidence is available in the manufacturer's response to the appraisal consultation document and the ERG critique.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bortezomib, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of bortezomib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee noted statements from the clinical specialists and patient experts that multiple myeloma is a complex and incurable disease associated with a range of comorbidities and complications. It was aware that survival rates were historically poor until the introduction of drugs such as bortezomib, thalidomide and lenalidomide, which improved survival and quality of life. The patient experts highlighted the relapsing and remitting nature of multiple myeloma, emphasising the importance of the availability of a range of treatment options and the flexibility to choose the most appropriate treatment for individual patients because the best induction regimen is chosen based on both disease- and patient-related factors. The clinical specialists commented that bortezomib-

based induction therapy would enable a higher proportion of patients to have a stem cell transplant and consequently experience longer progression-free survival and greater depth of response. The Committee also heard that bortezomib-based regimens were particularly valuable for people with clinically aggressive disease, but was aware that this group could not be clearly defined. The clinical specialists stated that induction treatment with bortezomib provides an important treatment option for patients with newly diagnosed multiple myeloma facing a high burden of disease, and when thalidomide is not a feasible treatment option because of contraindications. The Committee acknowledged the debilitating nature of the disease and the importance of having a range of treatment options available.

4.2 The Committee discussed the current management of multiple myeloma for people who are newly diagnosed and eligible for high-dose chemotherapy and stem cell transplantation. It heard from the clinical specialists that stem cell transplantation is considered the gold standard treatment for multiple myeloma because it is associated with improved progression-free survival, greater depth of response and therefore improved survival. It heard from the clinical specialists that in the UK clinicians use biological age, fitness and comorbidities rather than numerical age to decide eligibility for stem cell transplantation. The Committee noted that around 20–25% of all people with multiple myeloma would be fit enough for high-dose chemotherapy followed by a stem cell transplant. The clinical specialists stated that the aim of induction therapy was to enable more people to have stem cell transplantation successfully. The clinical specialists stated that current standard induction therapy in the UK was the combination of cyclophosphamide, thalidomide and dexamethasone, and that although vincristine, doxorubicin and dexamethasone had been

used in the past, this regimen is no longer used; in line with the guideline from the British Committee for Standards in Haematology on the diagnosis and management of multiple myeloma.

4.3 The Committee was aware that the manufacturer's submission included a comparison of bortezomib and dexamethasone against vincristine, doxorubicin and dexamethasone. It noted that this was not a relevant comparison because it was not in line with UK clinical practice and was outside the NICE scope of the appraisal, which specified thalidomide-containing regimens as comparators. The Committee was also aware that the manufacturer did not present a comparison of bortezomib, thalidomide and dexamethasone against cyclophosphamide, thalidomide and dexamethasone, but instead presented a comparison of bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone, assuming clinical equivalence between thalidomide and dexamethasone, and cyclophosphamide, thalidomide and dexamethasone. The clinical specialists stated the 2 regimens could be considered broadly similar. However, they stated that the advantage of using a triple therapy such as cyclophosphamide, thalidomide and dexamethasone was that there was more flexibility to reduce doses in the case of toxicity. The Committee queried whether thalidomide and dexamethasone is used in UK clinical practice and heard that the cyclophosphamide, thalidomide and dexamethasone regimen is the standard induction treatment in the UK. The Committee considered that the cyclophosphamide, thalidomide and dexamethasone regimen was the most appropriate comparator. It was persuaded that the manufacturer's threshold analyses demonstrated that the addition of cyclophosphamide would have to add a clinically implausible level of additional benefit (almost double) before the ICER for bortezomib, thalidomide and dexamethasone increased above

£30,000 per QALY gained compared with cyclophosphamide, thalidomide and dexamethasone (see section 3.37). Therefore the Committee concluded that bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone was a reasonable basis for appraising the clinical and cost effectiveness of bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone.

Clinical effectiveness

4.4 The Committee noted that the manufacturer presented evidence on the clinical effectiveness of bortezomib from the PETHEMA, GIMEMA, HOVON and IFM trials. The Committee was aware that the HOVON trial included the bortezomib, doxorubicin and dexamethasone regimen, which was not included in the bortezomib marketing authorisation. It therefore excluded it from its clinical and cost-effectiveness discussions. It noted that the trials included different regimens of bortezomib and had different study designs. The Committee noted that in the GIMEMA trial patients only received 3 cycles of bortezomib, thalidomide and dexamethasone whereas in the PETHEMA trial patients received 6 cycles, which was more in line with the marketing authorisation. Moreover, the Committee noted that the PETHEMA and GIMEMA trials differed in the number of stem cell transplants given and the type of consolidation (intensification therapy to sustain remission before lower-dose maintenance therapy) and maintenance treatments used after transplant, and that consolidation and maintenance treatment was not standard clinical practice in the NHS. The Committee was aware that none of the trials included a comparison with cyclophosphamide, thalidomide and dexamethasone, which is standard clinical practice in England.

4.5 The Committee discussed the results from the PETHEMA and IFM trials. It noted that in the PETHEMA trial, bortezomib, thalidomide and dexamethasone was associated with a statistically significant gain in overall response rate after induction compared with thalidomide and dexamethasone (84.6% compared with 61.4%, p<0.001) and that this was maintained after stem cell transplant (77.7% compared with 56.7%, p<0.001). The Committee also noted that, in the IFM trial, bortezomib and dexamethasone was associated with a similar gain in overall response rate compared with vincristine, doxorubicin and dexamethasone (77.1% compared with 60.7%, p<0.001) but a statistically significant difference was not shown after stem cell transplantation (79.6% compared with 74.4%, p=0.179). It noted that progression-free survival was longer in the bortezomib, thalidomide and dexamethasone arm of the PETHEMA trial than in the thalidomide and dexamethasone arm, and that the difference was statistically significant (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.45 to 0.92, p=0.015). It further noted that progression-free survival was longer in the bortezomib and dexamethasone arm of the IFM trial than in the vincristine, doxorubicin and dexamethasone arm, but the difference was not statistically significant (HR 0.88, 95% CI 0.70 to 1.11, p value not reported). The Committee agreed that induction treatment with bortezomib and dexamethasone was associated with statistically significant improvements in post-induction overall response rates compared with vincristine, doxorubicin and dexamethasone, and that induction treatment with bortezomib, thalidomide and dexamethasone resulted in statistically significant improvements in overall response rates (post-induction and post-stem cell transplant) and progression-free survival compared with thalidomide and dexamethasone. However, it concluded that no direct evidence was available to compare the efficacy of

bortezomib, thalidomide and dexamethasone or bortezomib and dexamethasone against cyclophosphamide, thalidomide and dexamethasone, the comparator regimen considered to be current standard care in the UK and therefore the most relevant comparator for the Committee's decision-making.

4.6 The Committee considered the unadjusted overall survival reported in the manufacturer's submission for the PETHEMA and IFM trials. It noted that median overall survival was not reached in either the PETHEMA trial (bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, hazard ratio 0.80, 95% CI 0.48 to 1.34, p=0.393) or the IFM trial (bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone, HR 0.8, 95% CI 0.54 to 1.19, p value not reported) and there was no statistically significant difference in overall survival between the treatment arms in each study. The Committee heard from the manufacturer and from the clinical specialists that the duration of the trials was too short to allow differences in overall survival to be seen between treatment groups. The clinical specialists also stated that given the differences in trial design relating to the numbers of stem cell transplants and types of maintenance treatment received it was not possible to draw firm conclusions. The Committee concluded that although there was uncertainty in the magnitude of overall survival associated with bortezomib, it was plausible that bortezomib's impact on induction response could be associated with improved overall survival.

4.7 The Committee considered the manufacturer's indirect comparison. It acknowledged the manufacturer's rationale that a network could not be formed to conduct an indirect comparison between the available trials and assumptions to overcome the network

limitations would generate considerable uncertainties and unreliable results. At the appraisal consultation stage, the Committee requested further analysis comparing single arms of the available trials, adjusting for the differences between the trial designs and baseline characteristics of the patients included in each study. The Committee concluded that although there would be limitations to this approach, further analysis from the manufacturer would provide useful comparative data to draw conclusions on the relative effectiveness of bortezomib, thalidomide and dexamethasone, and bortezomib and dexamethasone, compared with the most relevant comparator cyclophosphamide, thalidomide and dexamethasone, or an alternative comparator in situations in which the cyclophosphamide, thalidomide and dexamethasone regimen is considered inappropriate.

4.8 The Committee considered the adverse events associated with using a bortezomib-containing regimen. It heard from the clinical specialists that intravenously administered bortezomib had been associated with peripheral neuropathy, but that rapid dose reductions could effectively manage it. In addition, the clinical specialists highlighted that although the evidence presented was for intravenously administered bortezomib, the introduction of a subcutaneous formulation has substantially reduced the side effects related to peripheral neuropathy and also reduced the need for thromboprophylaxis. The Committee concluded that the adverse event profile of bortezomib was manageable (for full details of adverse reactions and contraindications, see the summary of product characteristics).

Cost effectiveness

4.9 The Committee considered the structure, assumptions and results of the manufacturer's economic model, which was based on data

from the PETHEMA and IFM trials for the bortezomib, thalidomide and dexamethasone and the bortezomib and dexamethasone regimens respectively. The Committee was aware that the model only provided comparisons for bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone and for bortezomib and dexamethasone against vincristine, doxorubicin and dexamethasone, which was not in line with current clinical practice in the UK, and that the vincristine, doxorubicin and dexamethasone regimen was outside of the scope of this appraisal. The Committee acknowledged that there was no direct evidence available to compare the bortezomib, thalidomide and dexamethasone and the bortezomib and dexamethasone regimens with cyclophosphamide, thalidomide and dexamethasone, and it asked the manufacturer to further explore this by conducting a further indirect comparison using single arms from the relevant clinical trials.

4.10 The Committee considered the manufacturer's approach to using post-induction rates from the PETHEMA and IFM trials in the economic model for the bortezomib, thalidomide and dexamethasone and the bortezomib and dexamethasone regimens respectively. It noted the ERG's comments that data from the MRC Myeloma VII trial used by the manufacturer to estimate long-term survival related to maximal response to treatment rather than post-induction response rate and therefore using post-stem cell transplant response rates from the PETHEMA and IFM trials might better predict progression-free survival and overall survival. The clinical specialists stated that post-stem cell transplant response rates would be more appropriate as long as they were based on an intention-to-treat analysis that included all people who were randomised in the trials regardless of whether they received treatment or not; however, if they were based only on patients who

received a transplant, post-induction response rates would be more meaningful. The ERG confirmed that post-stem cell transplant rates in both the PETHEMA and GIMEMA trials were based on an intention-to-treat analysis. The Committee concluded that using post-stem cell transplant response rates rather than post-induction response rates was more appropriate.

4.11 The Committee considered the way in which long-term survival had been extrapolated in the manufacturer's model. The Committee was aware that that the model extrapolated level of response after induction therapy to long-term survival and time to progression based on data from the MRC Myeloma VII trial. It noted the ERG's comments that the MRC Myeloma VII trial was not very recent because it had recruited patients between 1993 and 2003, and that its rates for overall survival and progression-free survival were likely to be lower than would be seen in current clinical practice. The Committee was also aware that although long-term survival end points had not been reached in the PETHEMA and IFM trials, the data available in these trials suggested that the manufacturer's model, using data from MRC Myeloma VII, underestimated overall survival. It noted that other data were available (for example, from a study by Alvares and the NMSG 5/94 study) that fit better with the data observed in the PETHEMA and IFM trials. The Committee concluded that the ERG's exploratory analysis using data from the Alvares and NMSG 5/94 studies was appropriate (see section 3.34) for estimating long-term survival and should be considered together with the analysis based on the MRC Myeloma VII study.

4.12 The Committee considered the costs used in the manufacturer's economic model. It was aware that the clinical trials were all conducted using intravenously administered bortezomib, and it heard from the manufacturer that this was also assumed in the

economic model and was therefore associated with a day-patient cost. The Committee was, however, aware that bortezomib is available as a subcutaneous formulation which is widely used and would therefore only be associated with an outpatient cost. The Committee also noted the comments from the clinical specialists that the subcutaneous formulation could reduce the risk of peripheral neuropathy and also reduce the need for thromboprophylaxis. The Committee considered that these issues combined might reduce the total cost of bortezomib in the model. The manufacturer updated the model to reflect this during consultation to reduce costs from £203 to £197 for first attendance and from £284 to £211 for subsequent visits.

4.13 The Committee noted that the manufacturer's comparison of bortezomib and dexamethasone with vincristine, doxorubicin and dexamethasone was outside the NICE scope because the comparator did not contain thalidomide, and in addition, the clinical specialists commented that the vincristine, doxorubicin and dexamethasone regimen is no longer used as an induction therapy for multiple myeloma in the UK. The Committee decided, therefore, that it was not appropriate to consider the results from this comparison. However, the Committee also noted that the bortezomib and dexamethasone regimen had a lower acquisition cost than the bortezomib, thalidomide and dexamethasone regimen as it did not include thalidomide, and heard from clinical specialists that it would provide a valuable treatment option, especially for patients who cannot tolerate thalidomide. The Committee was aware that the ERG's exploratory analyses also included comparisons of bortezomib and dexamethasone against thalidomide and dexamethasone, and comparisons of bortezomib and dexamethasone against cyclophosphamide, thalidomide and dexamethasone. Based on the analyses incorporating the Alvares

survival data and post-stem cell transplant response rates that were preferred by the Committee for the bortezomib, thalidomide and dexamethasone analysis, the Committee noted that the ERG's exploratory ICER for bortezomib and dexamethasone compared with thalidomide and dexamethasone was £26,700 per QALY gained. It also noted that in the comparison of bortezomib and dexamethasone with cyclophosphamide, thalidomide and the dexamethasone, the bortezomib and dexamethasone regimen was dominated by (that is, it was more costly and less effective than) cyclophosphamide, thalidomide and dexamethasone. The Committee acknowledged the lack of an appropriate comparison in the manufacturer's submission and the caveats surrounding the ERG's exploratory analysis, and asked the manufacturer to further explore the cost effectiveness of the bortezomib and dexamethasone (see section 4.15).

4.14 The Committee noted the manufacturer's original comparison of bortezomib, thalidomide and dexamethasone with thalidomide and dexamethasone, which resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £20,500 per QALY gained, and that the manufacturer had not presented probabilistic ICERs. The Committee then discussed the results of the ERG's exploratory analyses. The Committee noted that using post-stem cell transplant response rates instead of post-induction response rates (see section 4.10) resulted in an ICER of £26,300 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The Committee also noted that using data from the Alvares study instead of the MRC Myeloma VII study to model long-term survival resulted in an ICER of £30,400 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The clinical specialists raised concerns that the Alvares study was retrospective

in design and also quite old and therefore a more recent study would be more appropriate. The ERG confirmed that it had also conducted an exploratory analysis based on data from the NMSG 5/94 study and that this resulted in an ICER higher than £30,400 per QALY gained, that but this did not include the discontinuation rule and was therefore not presented (see section 3.34). The Committee noted that given the disparity between the overall survival results from the trials and those in the model, using an alternative data source such as the Alvares study, which was a better fit to the trial data, was appropriate. The Committee noted that incorporating post-stem cell transplant rates and using the Alvares study to inform overall survival together resulted in an ICER of £39,000 per QALY gained for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone. The Committee concluded that based on the analyses that were available before the appraisal consultation document was released, the ERG's exploratory analyses were appropriate and that £39,000 per QALY gained was an appropriate starting point for discussion on the most plausible ICER for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone.

4.15 The Committee was aware of the ERGs further exploratory analyses on bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone. The Committee understood that there were limitations with this approach because the data were drawn from a range of heterogeneous studies containing different comparators and different study designs and therefore could not be directly compared. Moreover, differences in trial design and baseline characteristics had not been taken into account. The Committee noted that this approach resulted in an ICER of £228,200 per QALY gained for bortezomib, thalidomide and dexamethasone compared

with cyclophosphamide, thalidomide and dexamethasone when using the manufacturer's base-case assumptions. Applying post-stem cell transplant response rates and survival data from the Alvares study resulted in an ICER of £82,000 per QALY gained for bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone. The Committee agreed that although there was considerable uncertainty associated with such an approach, the ICER based on the analyses that were available before the appraisal consultation document was released for bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone was likely to be higher than the ICER of £39,000 per QALY gained compared with thalidomide and dexamethasone. The Committee considered that further analyses were needed to explore the cost effectiveness of the bortezomib and dexamethasone regimen and asked the manufacturer to present:

- An indirect comparison of bortezomib in combination with dexamethasone, compared with cyclophosphamide in combination with thalidomide and dexamethasone, and compared with an alternative comparator in circumstances in which cyclophosphamide in combination with thalidomide and dexamethasone is not suitable. In the absence of a network to facilitate a robust comparison, the Committee requested that this should be a careful comparison using single arms from relevant clinical trials, taking into account differences in trial design and baseline characteristics. It should include sensitivity analyses using assumptions suggested by the Evidence Review Group:
  - using data from wider sources than the MRC Melanoma VII trial, including the Alvares and NMSG 5/94 studies, and

extrapolation from the trials of bortezomib-containing regimens to inform overall survival in the economic model
  - using post-stem cell transplant response rates from the IFM trial rather than post-induction response rates
  - using transplant rates by response category rather than total stem cell transplant rates
  - updated costs to reflect the use of a subcutaneous formulation of bortezomib.
- Probabilistic incremental cost-effectiveness ratios for the revised comparisons.

4.16 The Committee considered the manufacturer's response to the appraisal consultation document that included changes to the economic models for all the bortezomib regimens (see section 3.38). The Committee considered the manufacturer's revised modelling assumption that incorporated an 11.8 month survival benefit for people who received a stem cell transplant. The Committee noted that the model included survival curves for complete responders in addition to the assumption of survival benefit from receiving a stem cell transplant and discussed whether this amounted to double counting. It heard from the clinical specialists that incorporating the additional survival benefit was not double counting because the purpose of a stem cell transplant is to increase the depth of response, which could provide additive effect resulting in a survival benefit of up to a year. The Committee heard from the manufacturer that the additional survival benefit assumption was not a key driver of cost effectiveness because removing this benefit had minimal effect on the ICERs. The Committee concluded that the manufacturer's approach to modelling stem cell transplant benefit was acceptable for its decision making.

4.17 The Committee was aware that the manufacturer used the stem cell transplant rates from the PETHEMA trial to inform the comparison of bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone (80.8% and 61.4% respectively) but that other bortezomib trials (GIMEMA, HOVON and IFM) indicated rates were above 80% regardless of the treatment arm. The Committee was also aware that transplant rates for the comparison of bortezomib and dexamethasone (without thalidomide) against cyclophosphamide, thalidomide and dexamethasone, were incorporated from the IFM trial for the bortezomib and dexamethasone arm (89.1%) and from the MRC Myeloma IX trial for the cyclophosphamide, thalidomide and dexamethasone arm (66.7%). The Committee noted the ERG's concerns that this was inconsistent with transplant rates taken from the control arm of the IFM trial (81.8%, which was directly comparable and would be expected to be no better than a cyclophosphamide, thalidomide and dexamethasone control arm). The Committee noted that the ERG had explored the impact of incorporating a stem cell transplant rate of 81.8%, which resulted in the manufacturer's revised base-case ICER increasing from £20,588 to £36,700 per QALY gained. The Committee discussed whether the differences in the transplant rates were too wide for both comparisons. It heard from the clinical specialists that in clinical practice cyclophosphamide, thalidomide and dexamethasone was associated with a stem cell transplant rate of approximately 50% and this was corroborated by 2 large population-based studies. The clinical specialists stated that bortezomib regimens were likely to be associated with stem transplant rates of 60–65%. The clinical specialists also suggested that stem cell transplant rates should better reflect complete response rates than the control arms of the other trials suggest.

The Committee agreed that although a bortezomib regimen might be expected to improve the rate of stem cell transplant, it would be to a lesser extent than was modelled by the manufacturer, and more closely linked to response in clinical practice. However, the Committee also agreed that the differences in transplant rates between treatment arms in the models were plausible. The Committee concluded that although the impact of stem cell transplant rates included in the model on cost-effectiveness results was uncertain, it was unlikely to undermine the manufacturer's base-case cost-effectiveness results.

4.18 The Committee discussed the overall survival modelling informing the manufacturer's revised ICERs for the comparison of bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone. It noted that the manufacturer preferred the MRC Myeloma VII data as the source for long-term survival, which resulted in an ICER of £17,800 per QALY gained. The Committee heard from the ERG that the MRC Myeloma VII data did not fit the observed PETHEMA data. The Committee was aware that incorporating data from the ERG's preferred Alvares and NMSG 5/94 studies resulted in ICERs of £22,700 and £39,600 per QALY gained respectively. The manufacturer stated that caution should be taken in interpreting the fit with PETHEMA trial data beyond 30 months because of the level of censoring. The Committee questioned why data from the PETHEMA trial had not been used directly. The manufacturer argued that the data were immature. The Committee also heard from the clinical specialists that because patients in the PETHEMA trial could receive bortezomib as maintenance treatment (which is not standard practice in the UK) there would be substantial convergence between the treatment arms when more long-term survival data become available. The Committee recognised that even though there was little face validity

in the modelling of survival, it appreciated that the Kaplan−Meier curve from the PETHEMA trial was confounded by post-induction treatment. The Committee noted that incorporating only the NMSG 5/94 data resulted in ICERs that would not normally be considered to be cost effective (above £30,000 per QALY gained). The Committee considered concerns raised by the manufacturer and consultees that the NMSG study did not provide fully relevant data because it did not report median overall survival for partial and non-responders. The Committee concluded that using data from the NMSG 5/94 study would represent a pessimistic scenario and that the ICERs based on survival data from the MRC Myeloma VII (£17,800 per QALY gained) and Alvares (£22,700 per QALY gained) studies were appropriate for its decision making.

4.19 The Committee considered the manufacturer's ICERs for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone, as requested in the appraisal consultation document. It noted that using the MRC Myeloma VII, Alvares and NMSG 5/94 data sources to inform overall survival in the model resulted in ICERS of £20,600, £24,300 and £33,400 per QALY gained respectively. It noted that only using the NMSG 5/94 study data resulted in ICERs above £30,000 per QALY gained. Having discussed the concerns around the NMSG 5/94 data (see section 4.18), the Committee considered that results based on these data were likely to represent a pessimistic scenario. The Committee also considered the analyses presented by manufacturer when cyclophosphamide, thalidomide and dexamethasone may not be suitable, noting that vincristine, doxorubicin and dexamethasone was included as the most appropriate comparator in this situation. The Committee noted that the ICERs ranged from £18,900 per QALY gained using MRC Myeloma VII survival data to £25,600 using survival data from the

Alvares study. The Committee concluded that most plausible ICERs based on survival data from the MRC Myeloma VII and Alvares studies were appropriate for its decision making.

4.20 The Committee remained concerned that the modelling was subject to uncertainties, and that the manufacturer had also not provided sufficient external and internal validity. However, the Committee acknowledged that bortezomib regimens had a clear advantage with respect to induction response and that a link between improved response and survival was plausible. In particular, the Committee considered that there were people with clinically aggressive disease, with organ function at risk, or at risk of irreversible renal damage, who would benefit from a fast response associated with treatment with bortezomib, but heard that this group could not be categorically defined. Taking into account its consideration that the uncertainty around stem cell transplant rates was not likely to have a substantial impact on the ICER (section 4.16) and taking into consideration ICERs based on survival data from the MRC Myeloma VII and Alvares studies, the Committee concluded that, on balance, the ICERs for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, and for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone and compared with vincristine, doxorubicin and dexamethasone, were likely to be below £30,000 per QALY gained. Therefore both bortezomib regimens could be considered a cost-effective use of NHS resources.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation	Section
Key conclusion		

Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. The Committee was concerned that the modelling was subject to uncertainties, however it acknowledged that bortezomib regimens had a clear advantage with respect to induction response and that a link between improved response and survival was plausible. For the cost-effectiveness analysis, and in response to consultation, the manufacturer presented additional evidence that included changes to the economic models and comparisons with cyclophosphamide, thalidomide, and dexamethasone, the comparator regimen considered to be current standard care in the UK. Based on a threshold analysis presented by the manufacturer, the Committee concluded that bortezomib, thalidomide, and dexamethasone compared with thalidomide and dexamethasone was a reasonable basis for appraising the clinical and cost effectiveness of bortezomib, thalidomide, and dexamethasone compared with cyclophosphamide, thalidomide, and dexamethasone. The Committee considered and explored a range of ICERs using several studies included in the submissions, and concluded that, on balance, the ICERs for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, and for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone and compared with vincristine, doxorubicin and dexamethasone, were likely to be below £30,000 per QALY gained.		1.1 4.16-4.20
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from clinical specialists that stem cell transplantation is considered the gold standard treatment for multiple myeloma because it is associated with improved progression-free survival, greater depth of response and therefore improved survival. The clinical specialists stated that the aim of induction therapy was to enable more people to proceed to stem cell transplantation successfully.	4.2

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The clinical specialists commented that bortezomib-based induction therapy would enable a higher proportion of patients to have a stem cell transplant and consequently experience longer progression-free survival and greater depth of response. The Committee also heard that bortezomib-based regimens were particularly valuable for people with clinically aggressive disease, but was aware that this group could not be clearly defined. The Committee agreed that induction treatment with bortezomib and dexamethasone was associated with statistically significant improvements in post-induction overall response rates compared with vincristine, doxorubicin and dexamethasone, and that induction treatment with bortezomib, thalidomide and dexamethasone resulted in statistically significant improvements in overall response rates (post-induction and post-stem cell transplantation) and progression-free survival compared with thalidomide and dexamethasone. However, it concluded that no direct evidence was available to compare the efficacy of bortezomib, thalidomide and dexamethasone or bortezomib and dexamethasone with cyclophosphamide, thalidomide and dexamethasone, the comparator regimen considered to be current standard care in the UK and therefore the most relevant comparator for the Committee's decision-making.	4.1, 4.5
What is the position of the treatment in the pathway of care for the condition?	The clinical specialists stated that induction treatment with bortezomib provides an important treatment option for patients with newly diagnosed multiple myeloma, and when thalidomide is not a feasible treatment option because of contraindications.	4.1
Adverse reactions	Clinical specialists highlighted that although the evidence presented was for intravenously administered bortezomib, the introduction of a subcutaneous formulation has substantially reduced the side effects related to peripheral neuropathy and also reduced the need for thromboprophylaxis. The Committee concluded that the adverse event profile of bortezomib was manageable (for full details of adverse reactions and contraindications, see the summary of product characteristics).	4.8

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the manufacturer presented evidence on the clinical effectiveness of bortezomib from the PETHEMA, GIMEMA, HOVON and IFM trials. The Committee was aware that the HOVON trial included the bortezomib, doxorubicin and dexamethasone regimen, which was not included in the bortezomib marketing authorisation. It therefore excluded it from its clinical and cost-effectiveness discussions. The Committee noted that the trials included different regimens of bortezomib and had different study designs. It noted that in the GIMEMA trial patients only received 3 cycles of bortezomib, thalidomide and dexamethasone whereas in the PETHEMA trial patients received 6 cycles, which was more in line with the marketing authorisation. Moreover, the Committee noted that the PETHEMA and GIMEMA trials differed in the number of stem cell transplants given and the type of consolidation (intensification therapy to sustain remission before lower dose maintenance therapy) and maintenance treatments used after transplant, and that consolidation and maintenance treatment was not standard clinical practice in the NHS. The Committee was aware that none of the trials included a comparison with cyclophosphamide, thalidomide and dexamethasone, which is standard clinical practice in England.	4.4
Relevance to general clinical practice in the NHS	The Committee noted that the PETHEMA and GIMEMA trials differed in the number of stem cell transplants and the type of consolidation and maintenance treatments used after transplant and that consolidation and maintenance treatment was not standard clinical practice in the NHS. The Committee was aware that none of the trials included a comparison with cyclophosphamide, thalidomide and dexamethasone which is standard clinical practice in England. Moreover, the IFM trial included a comparison of bortezomib and dexamethasone with vincristine, doxorubicin and dexamethasone, which is no longer used.	4.4, 4.2

Uncertainties generated by the evidence	The Committee concluded that no direct evidence was available to compare the efficacy of bortezomib, thalidomide and dexamethasone or bortezomib and dexamethasone against cyclophosphamide, thalidomide and dexamethasone, the comparator regimen considered to be current standard care in the UK and therefore the most relevant comparator for the Committee's decision-making. The Committee heard from the manufacturer and from the clinical specialists that the duration of the trials was too short to allow differences in overall survival to be seen between treatment groups. It concluded that although there was uncertainty in the magnitude of overall survival gain associated with bortezomib, it was plausible that bortezomib's impact on induction response could be associated with improved overall survival.	4.5, 4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None	

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that in the PETHEMA trial, bortezomib, thalidomide and dexamethasone was associated with statistically significant gain in overall response rate post-induction compared with thalidomide and dexamethasone (84.6% compared with 61.4%, p<0.001) and that this was maintained after stem cell transplant (77.7% compared with 56.7%, p<0.001). The Committee also noted that, in the IFM trial, bortezomib and dexamethasone was associated with a similar gain in overall response rate compared with vincristine, doxorubicin and dexamethasone (77.1% compared with 60.7%, p<0.001) but a statistical difference was not shown after stem cell transplant (79.6% compared with 74.4%, p=0.179). The Committee noted that median overall survival was not reached in either the PETHEMA trial (bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, hazard ratio 0.80, 95% 0.48 to 1.34, p=0.393) or IFM trial (bortezomib and dexamethasone compared with vincristine, doxorubicin and dexamethasone, HR 0.8, 95% CI 0.54 to 1.19, p value not reported) and there was no statistically significant difference in overall survival between the treatment arms in each study. It concluded that although there was uncertainty in the magnitude of overall survival gain associated with bortezomib, it was plausible that bortezomib's impact on induction response could be associated with improved overall survival.	4.5, 4.6
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	Not applicable.	

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee was aware that the model only provided comparisons for bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone and for bortezomib and dexamethasone against vincristine, doxorubicin and dexamethasone, which was not in line with current clinical practice in the UK, and that the vincristine, doxorubicin and dexamethasone regimen was outside of the scope of this appraisal. The Committee acknowledged that there was no direct evidence available to compare the bortezomib, thalidomide and dexamethasone and the bortezomib and dexamethasone regimens with cyclophosphamide, thalidomide and dexamethasone, and it asked the manufacturer to further explore this by conducting a further indirect comparison using single arms from the relevant clinical trials.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted the ERG's comments that the MRC Myeloma VII trial was not very recent because it recruited patients between 1993 and 2003, and its rates for overall survival and progression-free survival were likely to be lower than would be seen in current clinical practice. The Committee was also aware that although long-term survival end points had not been reached in the PETHEMA and IFM trials, the data available in these trials suggested that the manufacturer's model, using data from MRC Myeloma VII, underestimated overall survival. The Committee concluded that although the impact of stem cell transplant rates included in the model on cost-effectiveness results was uncertain, it was unlikely to undermine the manufacturer's base-case cost-effectiveness results.	4.11, 4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been	The manufacturer selected the van Agthoven study as the base-case source of utility values because the utility values were obtained using EQ-5D. With regard to adverse events the manufacturer applied a disutility of 0.02 to each patient experiencing an adverse event associated with induction therapy.	3.24

identified that were not included in the economic model, and how have they been considered?	The Committee noted the comments from the clinical specialists that the subcutaneous formulation could reduce the risk of peripheral neuropathy and also reduce the need for thromboprophylaxis. The Committee considered that these issues combined might reduce the total cost of bortezomib in the model.	4.12
Are there specific groups of people for whom the technology is particularly cost effective?	No.	
What are the key drivers of cost effectiveness?	The manufacturer's deterministic sensitivity analyses highlighted that the results were most sensitive to the mortality for patients who had a complete response after the induction therapy, and to drug costs.	3.26
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, the manufacturer's base-case using the MRC Myeloma VII data as the source for long-term survival ICER resulted in an ICER of £17,800 per QALY gained. The Committee was aware that incorporating data from the ERG's preferred Alvares and NMSG 5/94 studies resulted in ICERs of £22,700 and £39,600 per QALY gained respectively.	4.18
	For bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone, using the MRC Myeloma VII, Alvares and NMSG 5/94 data sources to inform overall survival in the model, the ICERs were £20,600, £24,300 and £33,400 per QALY gained respectively. The Committee concluded that the ICERs based on survival data from the MRC Myeloma VII and Alvares study were appropriate for its decision making.	4.19

For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	Not applicable	
Additional factors taken into account		
Patient access schemes (PPRS)	None submitted.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendations were raised.	

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 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has newly diagnosed multiple myeloma and the doctor responsible for their care thinks that bortezomib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- 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 publication. Further information is available on the NICE website.

- Bortezomib and thalidomide for the first-line treatment of multiple myeloma. NICE technology appraisal guidance 228 (2011).

7 Review of guidance

7.1 The guidance on this technology will be considered for review in February 2017. 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 Stevens
Chair, Appraisal Committee
February 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.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Dr Andrew Burnett

Formerly - Director for Health Improvement and Medical Director, NHS Barnet, London

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Dr Maria Dyban

General Practitioner, Kings Road Surgery, Cardiff

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler

Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam

Lay Member

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Grant Maclaine

Formerly - Director, Health Economics & Outcomes Research, BD, Oxford

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School/Senior Clinical University Teacher, University of Glasgow

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Tim Stokes

Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden

Reader in Health Economic Modelling**,** School of Health and Related Research, University of Sheffield

Dr Judith Wardle

Lay Member

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.

Christian Griffiths

Technical Lead

Raisa Sidhu

Technical Adviser

Nicole Fisher

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Technology Assessment Centre:

- Cooper K, Hartwell D, Copley V et al. Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation: A Single Technology Appraisal. SHTAC. May 2013

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. Manufacturer/sponsor:

- Janssen

II. Professional/specialist and patient/carer groups:

- Myeloma UK
- South Asian Health Foundation
- British Society of Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Myeloma Forum

III. Other consultees:

- Department of Health
- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- Celgene
- Pfizer
- National Cancer Research Institute
- Southampton Health Technology Assessment Centre (SHTAC)
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

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

- Dr Jenny Bird, Consultant Haematologist, nominated by Royal College of Pathologists and British Society of Haematology – clinical specialist
- Professor Kwee Yong, Consultant Haematologist, nominated by UK Myeloma Forum, Royal College of Pathologists and British Society of Haematology – clinical specialist
- Eric Low, Chief Executive, nominated by UK Myeloma Forum – patient expert
- Stuart Fullerton, nominated by UK Myeloma Forum – patient expert

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

- Janssen