

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Bortezomib and thalidomide for the first-line treatment of multiple myeloma

1 Guidance

- 1.1 Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.
- 1.2 Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
- high-dose chemotherapy with stem cell transplantation is considered inappropriate **and**
 - the person is unable to tolerate or has contraindications to thalidomide.

2 Clinical need and practice

- 2.1 Multiple myeloma is a cancer of a type of white blood cell (plasma cell) in the bone marrow. In people with multiple myeloma, a single plasma cell becomes cancerous to form a myeloma cell, which begins to multiply. These abnormal plasma cells, or myeloma cells, build up in the bone marrow, reducing the space available for making normal white cells, red cells and platelets. Normal blood cells are responsible for fighting infections, carrying oxygen around the body and blood clotting. Myeloma cells produce large amounts

of one type of abnormal antibody, which does not work properly and is not able to fight infection. Symptoms and clinical features of multiple myeloma include fatigue, bone pain and/or fracture, anaemia, infections, M-protein in serum and/or urine, and hypercalcaemia. The origin of multiple myeloma is unknown and malignant cells display a variety of cytogenetic abnormalities.

- 2.2 Multiple myeloma is the second most common haematological cancer in the UK. In England and Wales there are approximately 3600 new diagnoses recorded annually. In 2007, most diagnoses were recorded in people aged 75–79 years. Multiple myeloma is about 1.5 times more common in men than in women, and twice as common in people of African or Caribbean descent. In the UK, the estimated lifetime risk of developing multiple myeloma is 1 in 148 for men and 1 in 186 for women. There are currently between 10,000 and 15,000 people living with multiple myeloma in the UK.
- 2.3 Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy. The aim of treatment is to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects. Survival after diagnosis can vary from months to more than 10 years. Factors affecting survival and outcome include burden of disease, type of cytogenetic abnormality, age and performance status, and response to treatment.
- 2.4 In England and Wales the choice of first-line treatment (that is, treatment for treatment-naïve patients) depends on a combination of factors. Most people with multiple myeloma are not able to withstand intensive treatment, such as high-dose chemotherapy with stem cell transplantation, because of their age, other health problems or poor performance status. These people are offered single-agent or combination chemotherapy, which is less intensive.

Typically, combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid (such as prednisolone or dexamethasone). More recent treatment options include drugs such as thalidomide and bortezomib. The main objective of first-line therapy is to achieve a period of stable disease (termed the plateau phase) for as long as possible, thereby prolonging survival and maximising quality of life. After initial treatment, most people usually experience a period of remission, but almost all relapse eventually, and some have disease that does not respond (is refractory) to treatment.

3 The technologies

Bortezomib

- 3.1 Bortezomib (Velcade, Janssen) is an anticancer drug that works by reversible proteasome inhibition. This inhibition leads to arrest of the cell cycle and apoptosis (cell death), which reduces tumour growth. Myeloma cells are more sensitive to the action of bortezomib than normal cells.
- 3.2 Bortezomib, in combination with melphalan and prednisone, is licensed for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant. Bortezomib is administered as an intravenous injection. Bortezomib is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In cycles 1–4, bortezomib is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In cycles 5–9, bortezomib is administered once weekly (days 1, 8, 22 and 29). Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each cycle.
- 3.3 Bortezomib treatment is associated with peripheral neuropathy, thrombocytopenia, gastrointestinal effects (diarrhoea, nausea,

vomiting and constipation) and other side effects. For full details of side effects and contraindications, see the summary of product characteristics (SPC).

- 3.4 The cost for a 3.5-mg vial of bortezomib is £762.38 (British national formulary [BNF] edition 61). Costs may vary in different settings because of negotiated procurement discounts.

Thalidomide

- 3.5 Thalidomide (Thalidomide Celgene, Celgene) is an immunomodulatory agent. Its precise mechanism of action is under investigation and is currently unknown, but it is thought to have multiple actions, including anti-inflammatory activity and the ability to inhibit the growth and survival of myeloma cells and the growth of new blood vessels. It is also a non-barbiturate hypnotic sedative with central action.
- 3.6 Thalidomide in combination with melphalan and prednisone is licensed 'as first-line treatment of patients with untreated multiple myeloma, aged \geq 65 years or ineligible for high dose chemotherapy'. The recommended dose is 200 mg daily, taken orally. A maximum number of 12 cycles of 6 weeks should be used. Thalidomide is prescribed and dispensed according to the Thalidomide Celgene Pregnancy Prevention Programme.
- 3.7 Thalidomide treatment is associated with thromboembolic events, peripheral neuropathy, rash/skin reactions, bradycardia, syncope and somnolence. Section 4.2 of the SPC outlines how to manage comorbidities such as risk of thromboembolic events, peripheral neuropathy or hepatic or renal impairment. For full details of side effects and contraindications, see the SPC.
- 3.8 The cost for a 28-capsule pack of 50-mg thalidomide capsules is £298.48 (BNF edition 61). Costs may vary in different settings

because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 *Clinical effectiveness*

4.1.1 In addition to the licensed indications of bortezomib and thalidomide, the remit of the scope allowed for inclusion of evidence from the ongoing UK-wide, Medical Research Council-sponsored Multiple Myeloma IX (MMIX) trial. This trial included thalidomide in combination with cyclophosphamide and attenuated dexamethasone, which is not a licensed indication for thalidomide. The appraisal investigated the following treatment strategies:

- thalidomide, melphalan and prednisolone/prednisone (MPT)
- thalidomide, cyclophosphamide and attenuated dexamethasone (CTDa)
- bortezomib, melphalan and prednisolone/prednisone (VMP).

Each was compared with melphalan or cyclophosphamide plus prednisolone/prednisone or dexamethasone.

The Assessment Group and manufacturers identified evidence on the clinical effectiveness of bortezomib and thalidomide against the relevant comparators within the licensed indications for each drug, and according to the appraisal scope.

MPT versus melphalan plus prednisolone/prednisone (MP)

4.1.2 The Assessment Group identified three randomised controlled trials (RCTs) (Intergroupe Francophone du Myélome [IFM] 99/06, IFM 01/01 and GIMEMA) that compared MPT with MP. The numbers of participants recruited to the studies were 447, 232

and 331 respectively. The two IFM studies differed in the target age range of participants: IFM 01/01 included people aged at least 75 years, whereas IFM 99/06 mainly included people aged between 65 and 75 years, with younger people being eligible for inclusion providing they were not eligible for high-dose chemotherapy. The GIMEMA study included people older than 65 years without specifying any upper age limit, but also included participants younger than 65 years providing they were unable to undergo high-dose chemotherapy with stem cell transplantation. The quality of the RCTs was variable and was difficult to determine in some cases because details needed for quality assessment were incompletely reported. The intention-to-treat analyses and the methods used to account for missing data were in general poorly described.

- 4.1.3 Overall survival was the primary outcome for IFM 99/06 and IFM 01/01. The secondary outcomes of these studies included response rates, progression-free survival and adverse events. The primary outcome measures for the GIMEMA study were response rates and progression-free survival. The secondary outcomes included overall survival and adverse events.
- 4.1.4 IFM 99/06 and IFM 01/01 reported a statistically significant increase in progression-free survival ($p = 0.001$) in the MPT group compared with the MP group. The IFM 99/06 study reported median progression-free survival of 27.5 months (standard error [SE] = 2.1) for the MPT group compared with 17.8 months (SE = 1.4) for the MP group at a median follow-up of 51.5 months (difference of 9.7 months). The IFM 01/01 study reported median progression-free survival of 24.1 months (95% confidence interval [CI] 19.4 to 29.0) for the MPT group compared with 18.5 months (95% CI 14.6 to 23.1) for the MP group after a median follow-up of 47.5 months (difference of 5.6 months). Meta-analysis of the data

on progression-free survival confirmed that MPT was superior to MP for this outcome. The hazard ratio (HR) for progression-free survival from the meta-analysis was 0.56 (95% CI 0.46 to 0.67) in favour of MPT. The meta-analysis suggested that there was little or no heterogeneity between the two trials for this outcome.

- 4.1.5 The GIMEMA study included maintenance therapy with thalidomide after first-line treatment (that is, patients received six cycles of first-line treatment and if they responded and their condition did not progress, they received maintenance treatment continuously until relapse or the development of refractory disease). Because patients received maintenance therapy, overall survival, which was a secondary outcome in this study, was not eligible for inclusion in the Assessment Group's systematic review. IFM 99/06 and IFM 01/01 reported a statistically significant difference in overall survival in favour of the group receiving MPT. The IFM 99/06 study reported a median overall survival of 51.6 months (interquartile range [IQR] 26.6 to not reached) for the MPT group compared with 33.2 months (IQR 13.8 to 54.8) for the MP group after a median follow-up of 51.5 months. The IFM 01/01 study reported a median survival of 44 months (95% CI 33.4 to 58.7) in the group receiving MPT compared with 29.1 months (95% CI 26.4 to 34.9) in the group receiving MP. Meta-analysis of the data on overall survival from the two studies confirmed the superiority of MPT over MP. The HR for overall survival from the meta-analysis was 0.62 (95% CI 0.50 to 0.77) and showed that there was little or no heterogeneity between the two trials for this outcome.

- 4.1.6 Response to treatment (at 6 months) was a primary outcome of the GIMEMA study and a secondary outcome in IFM 99/06 and IFM 01/01. At 6 months, more participants in the MPT group had a complete response or a partial response or better (according to

European Group for Blood and Marrow Transplantation criteria). At 12 months, IFM 99/06 and IFM 01/01 reported that a statistically significantly greater proportion of participants had a complete response or at least a partial response. Complete response outcomes from the three studies were combined by meta-analysis, and this confirmed that MPT was superior to MP in terms of the proportion of patients achieving a complete response (relative risk [RR] 5.49, 95% CI 2.55 to 11.83).

- 4.1.7 Adverse events were difficult to summarise across the three studies because they were reported differently. Because the GIMEMA study included maintenance therapy with thalidomide, few data on adverse events from this study could be included in the Assessment Group's systematic review. Adverse events that occurred statistically significantly more often in the MPT arms of IFM 99/06 and IFM 01/01 included neutropenia and peripheral neuropathy. The IFM 99/06 study found that non-haematological adverse events of grade 3 or more were statistically significantly more likely in the MPT group ($p < 0.0001$). For thrombosis or embolism, somnolence and constipation, the results were inconsistent between IFM 99/06 and IFM 01/01, with no significant difference in incidence in the IFM 01/01 study and statistically significantly more of these events in the MPT group in the IFM 99/06 study. This inconsistency may be a result of the different methods of reporting adverse events.
- 4.1.8 The IFM 99/06 and IFM 01/01 studies provided data on second-line treatment that could be included in the Assessment Group's systematic review. In the IFM 99/06 study, 65% of the MP group received second-line treatment compared with 44% of the MPT group. The IFM 01/01 study reported disease progression in 156 participants overall, with more participants with disease progression in the MP group than the MPT group (72% versus

64%). Second-line treatment was received by a similar proportion of participants with disease progression in each arm. In both IFM 99/06 and IFM 01/01, thalidomide (alone or in combination with another agent) was the most common second-line treatment in the MP group, with about a fifth of participants in the MPT groups receiving thalidomide again as second-line therapy. In the IFM 99/06 study, the most common second-line treatment in the MPT group was a combination of vincristine, doxorubicin, and dexamethasone. Only 13% of participants in the MPT group received bortezomib. In contrast, IFM 01/01 reported that 31% of participants in the MPT group received bortezomib as a second-line treatment. Because the GIMEMA study included maintenance therapy with thalidomide after first-line treatment, data on second-line treatment were not eligible for inclusion in the Assessment Group's systematic review.

CTDa versus MP

4.1.9 The Assessment Group acknowledged an ongoing RCT, the MMIX trial, which compared CTDa with MP. People were eligible to participate if they had newly diagnosed symptomatic or non-secretory multiple myeloma and had not received previous treatment for myeloma (other than local radiotherapy). The non-intensive pathway of the MMIX study was designed for older (generally 70 years of age or older) or less fit participants (who could be younger than 70), but strict age restrictions were not in place. The primary outcomes were overall survival, progression-free survival and response. Secondary outcomes included quality of life and adverse events.

4.1.10 Some data from the MMIX study on overall survival, progression-free survival, adverse events and health-related quality of life were not eligible for inclusion in the Assessment Group's systematic review because participants were randomised to

receive either maintenance therapy with thalidomide or no maintenance therapy after they had completed first-line treatment. In response to a request from the Assessment Group, the MMIX trial management group provided data on overall survival, progression-free survival and response to treatment for participants who were excluded from the maintenance randomisation and for those randomised to receive no maintenance (that is, all people who received first-line only treatment were considered). The Assessment Group concluded that these additional data did not substantially alter the outcomes for the whole trial population because the data were immature and for a small number of patients. Although the data for participants receiving maintenance therapy were not included, the Committee considered very carefully data from the small number of participants who were randomised to receive no maintenance therapy.

- 4.1.11 Data on response rates from the MMIX study were eligible for inclusion in the Assessment Group's systematic review. Response was measured as complete, very good or partial. The principal investigators of the MMIX study identified data on response and adverse events as unpublished academic in confidence and therefore these data cannot be reported.

VMP versus MP

- 4.1.12 The Assessment Group identified one RCT (VISTA) comparing VMP with MP. People were eligible to participate if they had newly diagnosed, untreated, symptomatic, measurable myeloma and were not candidates for high-dose chemotherapy with stem cell transplantation because of their age (65 years or older) or coexisting conditions. Most, but not all, analyses had followed intention-to-treat principles, but the methods used to account for any missing data were not described.

4.1.13 The primary outcome was time to disease progression. Secondary outcomes included overall survival, progression-free survival, response, adverse events and health-related quality of life. Median time to subsequent myeloma therapy and treatment-free interval were 20.8 months and 9.4 months respectively in the group receiving MP; these were not reached in the group receiving VMP. Median time to disease progression was significantly longer in the VMP group than in the MP group (20.7 and 15 months respectively; HR = 0.54, $p < 0.001$). An advantage in terms of overall survival was reported for VMP compared with MP. A statistically significant survival benefit for VMP was reported after a median follow-up of 25.9 months (HR = 0.64, $p = 0.0032$). After a median follow-up of 36.7 months, 3-year survival rates were 68.5% versus 54% respectively. The most recent analyses showed a median overall survival of 43.1 months for participants receiving MP; it was not possible to estimate overall survival in the group receiving VMP because median overall survival had not been reached for VMP. After a median follow-up of 16.3 months, median progression-free survival was 21.7 months for the group receiving VMP compared with 15.2 months for the group receiving MP (HR = 0.56, $p < 0.001$). A number of response-to-treatment rates (including partial response and complete response) were reported as secondary outcomes. The time at which response was assessed was not reported. The proportion of participants with at least a partial response was 71% in the VMP group and 35% in the MP group ($p < 0.001$). The proportions with a complete response were 30% and 4% respectively ($p < 0.001$). The proportion with a partial response was 40% in the VMP group and 31% in the MP group, and the proportions with a minimal response were 9% and 22% respectively. The proportion with stable disease was 18% in the VMP group and 40% in the MP group, and the progressive

disease rates were 1% and 2% respectively.

4.1.14 Participants in both arms of the VISTA trial experienced adverse events. Although the occurrence of any adverse event and any grade 4 adverse event was similar in the two groups, there was a statistically significant increase in grade 3 adverse events in the group receiving VMP (53% versus 44%, $p = 0.02$).

Haematological events were the most frequently reported and were similar in the two groups. Peripheral sensory neuropathy was reported more frequently in the group receiving VMP, but at the time of the last analysis, 74% of peripheral neuropathy events had either resolved (56%) or decreased by at least one toxicity grade (18%) within a median of 2 months. All grade 3 and grade 4 gastrointestinal events were more frequent in the group receiving VMP (19% versus 5%, no p value given). The incidence of deep vein thrombosis was low and similar in the two groups.

4.1.15 Limited data on health-related quality of life were available. After best response, participants treated with VMP had a higher sustained improvement in 14 of the 15 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) scores than participants treated with MP.

4.1.16 Data on second-line treatment indicated that in the MP group 57% of participants started second-line treatment within 2 years compared with 38% in the VMP group. Over half of the participants in each group received either thalidomide or lenalidomide as a second-line treatment.

Summary of the clinical effectiveness

4.1.17 The Assessment Group concluded that the evidence from two studies (IFM 99/06 and IFM 01/01) indicated that MPT was more effective than MP in terms of increasing overall survival

(HR = 0.62, 95% CI 0.50 to 0.77) and the secondary outcome of progression-free survival (HR = 0.56, 95% CI 0.46 to 0.67). Three studies (IFM 99/06, IFM 01/01 and GIMEMA) provided evidence of a complete response in a statistically significantly greater proportion of participants receiving MPT (RR = 5.49, 95% CI 2.55 to 11.83). Adverse events occurred in both trial arms, but peripheral neuropathy and neutropenia were most consistently, and statistically significantly, associated with the use of thalidomide.

- 4.1.18 Data from the MMIX trial (CTDa versus MP) on response rates were eligible for inclusion in the Assessment Group's systematic review; however, overall survival and progression-free survival were not eligible for inclusion (see section 4.1.10).
- 4.1.19 The Assessment Group concluded that the evidence from one study (VISTA) indicated that combination chemotherapy with VMP was more effective than MP in terms of a longer time to disease progression, increasing overall survival and increasing the proportion of participants achieving a complete response. Adverse events occurred in both trial arms. Bortezomib was associated with a statistically significant increase in grade 3 adverse events.
- 4.1.20 Following consultation, the manufacturer of bortezomib submitted evidence of the effect on overall survival of the inclusion of studies with participants who had received maintenance therapy with thalidomide (GIMEMA, MMIX and two additional studies HOVON and NORDIC). For each study, the manufacturer plotted the HR of overall survival at cumulative time periods (3-month intervals). The HR was derived using all deaths up to that point but excluded further follow-up. The manufacturer stated that in all studies except IFM 99/06, the HR improved as follow-up increased, regardless of whether the studies included maintenance treatment or not. The Assessment Group commented on the additional

evidence and stated that it was not possible to make conclusions about the relative effects of maintenance versus first-line treatment from the evidence submitted.

4.2 Cost effectiveness

4.2.1 The two manufacturers submitted cost-effectiveness models. The Assessment Group developed its own economic model and critiqued the economic models submitted by the manufacturers.

The Celgene economic model

4.2.2 The manufacturer of thalidomide developed a Markov model to compare the costs and benefits of MPT with those of VMP and MP in people with multiple myeloma who are older than 65 years or are 'ineligible for high-dose chemotherapy'. The model had four health states that were defined by the stage of disease progression or the occurrence of adverse events. The four health states were: pre-progression without adverse events, pre-progression with adverse events, post-progression and death. The analysis was undertaken over a lifetime horizon (that is, 30 years). Treatment effects were calculated from a mixed-treatment comparison of data from three RCTs (VISTA, IFM 99/06, IFM 01/01), using measures of survival time before and after progression as the primary outcomes. Resources and costs were obtained from several sources, including an unpublished survey of UK haematologists by the manufacturer of thalidomide, NHS reference costs, and BNF edition 57 with costs inflated to 2008 values.

4.2.3 The manufacturer's model included the following assumptions:

- Post-progression survival was modelled to be the same across different treatment strategies, with the different arms assumed to receive the same alternative treatment after progression (that is,

second- and third-line treatments).

- Patients were assumed to discontinue first-line treatment on disease progression.
- No costs for second- and third-line treatments were included.
- Deaths occurred at or after progression and were assumed to be because of disease-related deterioration.
- Adverse events included in the model incorporated a utility decrement at the time of the event and the additional cost of treating them. They were assumed not to affect the rates of disease progression or overall survival, or treatment duration, efficacy or dose.

4.2.4 Data on health-related quality of life were obtained from an RCT (HOVON 24) of intensive chemotherapy followed by myeloablative therapy with autologous stem cell rescue compared with intensive chemotherapy alone. The utility values used were 0.64 for people not responding to treatment and 0.81 for people who did respond (using the utility value for the general population of the same age). A utility value of 0.77 at 24 months was used for people who continue to respond to intensive chemotherapy and whose disease has not progressed.

4.2.5 The base-case cost-effectiveness results were as follows:

- MPT compared with MP was associated with an incremental cost-effectiveness ratio (ICER) of £23,381 per quality-adjusted life year (QALY) gained based on an incremental effect of 0.85 QALYs and an incremental cost of £19,768.
- VMP compared with MPT was associated with an ICER of £303,845 per QALY gained based on an incremental effect of 0.07 QALYs and an incremental cost of £21,483.

4.2.6 One-way deterministic sensitivity analyses showed that the parameters with the greatest effect on the model results were

changes in treatment efficacy, with a range of £16,586 to £33,275 per QALY gained for MPT versus MP and a range of £148,873 to £1,000,435 per QALY gained for VMP versus MPT. Probabilistic sensitivity analysis was not conducted because the manufacturer considered the efficacy of MPT and VMP to be essentially the same and therefore the cost difference would be the key factor in the model.

The Janssen economic model

4.2.7 The manufacturer of bortezomib developed a decision-analytic cost–utility model to compare the costs and benefits for VMP with those of MPT, CTDa and MP in people with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with stem cell transplantation. The model included four health states: before response to treatment; response to treatment without progression; post-progression; and death. The times to response or death were estimated from life tables constructed directly from data from the VISTA trial. Progression-free survival at 6, 12, 18 and 24 months for MP was estimated from a meta-analysis of the MP arms of included RCTs. Progression-free survival was extrapolated beyond 24 months. Utility values for health-related quality of life were assigned to each of the states: 0.77 for before response to treatment; 0.81 for response to treatment without progression; and 0.64 for post-progression. The model used a cohort of people newly diagnosed with multiple myeloma, with MP as the baseline treatment. Treatment effects for VMP, MPT and CTDa were then modelled over time by adjusting the baseline results via HRs. HRs were estimated at 48 months for overall survival for each of the RCTs, except the VISTA trial, which had a follow-up of only 36-months. Overall survival for patients receiving thalidomide was estimated from five RCTs, some of which included thalidomide maintenance.

4.2.8 The manufacturer's model made the following assumptions:

- The resource use cost for the first-line management of multiple myeloma was the same for all regimens.
- Seven cycles of treatment with MP were used (as in the VISTA trial).
- For bortezomib, 31.5 vials were used per patient (as in the VISTA trial).
- A dose of thalidomide of 150 mg/day was used for the MPT regimen and 167 mg/day was used for the CTDa regimen.
- The costs of treating adverse events were included in the model; the incidence of adverse events does not influence the treatment duration, efficacy or patient utility.

4.2.9 Costs were included for second- and third-line treatments. On disease progression, it was assumed that second-line treatment would consist of bortezomib plus high-dose dexamethasone, CTDa or high-dose dexamethasone. Most people received CTDa after first-line VMP. People on other first-line therapies usually received bortezomib and high-dose dexamethasone as second-line treatment. All patients received lenalidomide plus dexamethasone as third-line treatment. Most people receiving bortezomib as first-line treatment would not receive it as second-line treatment.

4.2.10 The manufacturer's base-case cost-effectiveness results were as follows:

- MPT compared with MP was associated with an ICER of £8912 per QALY gained based on an incremental effect of 0.55 QALYs and an incremental cost of £4888.
- CTDa compared with MP was associated with an ICER of £10,905 per QALY gained based on an incremental effect of 0.21 QALYs and an incremental cost of £2234.

- VMP compared with MP was associated with an ICER of £10,498 per QALY gained based on an incremental effect of 1.17 QALYs and an incremental cost of £12,242.

4.2.11 One-way sensitivity analysis showed the model was most sensitive to the following parameters: underlying MP survival hazard, HRs for overall survival, dose of thalidomide, and duration of treatment with thalidomide in the MPT arm. A probabilistic sensitivity analysis showed that at the £20,000 and £30,000 thresholds, VMP has the highest probability of being cost effective (64% and 75% respectively).

4.2.12 Two scenario analyses were conducted. The first excluded the costs of subsequent therapy after first-line treatment. In this scenario, the cost-effectiveness results were less favourable for each of the treatments and the ICERs increased to £48,437, £16,956 and £21,099 per QALY gained for CTDa, MPT, and VMP respectively, compared with MP. The second scenario assumed the same second-line treatments as for people treated with MP in the VISTA trial. For this scenario, the results were similar to the base-case analyses.

The Assessment Group model

4.2.13 The Assessment Group's survival model was developed to estimate the costs, benefits and cost effectiveness of MPT, VMP and CTDa compared with MP, in people with newly diagnosed multiple myeloma who are 'ineligible' for high-dose chemotherapy with stem cell transplantation. The model consisted of cycles of 6 weeks in length to be consistent with the cycle lengths used for chemotherapy treatment. A lifetime horizon of 30 years was modelled. Survival was classified into three health states: treatment (defined as the time patients are treated with first-line therapy); post-treatment (defined as the mean time from the end

of first-line treatment until disease progression) and post-progression (defined as the mean time from disease progression until death).

- 4.2.14 The Assessment Group constructed a survival curve for overall survival and a curve for progression-free survival for each of the alternative treatments (MPT, MP, VMP) included in its systematic review (see sections 4.1.4, 4.1.5 and 4.1.13). These curves were used to derive the time spent in the three health states. For each treatment option, the relative risk for complete response compared with MP was derived from the outcome data for complete response from the RCTs included in the Assessment Group's systematic review (see sections 4.1.6, 4.1.11 and 4.1.13).
- 4.2.15 Health-related quality of life data were from a systematic review of studies of health-related quality of life. The Assessment Group did not identify any generic preference-based studies of people with untreated multiple myeloma who were not eligible for high-dose chemotherapy with stem cell transplantation, but did identify a study not identified by the manufacturers that assessed health-related quality of life in this group using the EORTC QLQ-C30. The Assessment Group mapped the EORTC QLQ-C30 to the EQ-5D using a validated mapping algorithm. The utility estimates used were 0.58 for the treatment health state and 0.68 for the post-treatment state.
- 4.2.16 Costs were derived from a number of sources including the BNF, RCTs included in the Assessment Group's systematic review and clinical and expert clinical opinion. The Assessment Group's model included the following assumptions:
- For bortezomib, each person receives one vial per administration.
 - Patients receive second-line treatment following disease

progression after first-line therapy. The model assumed that most people who received VMP as first-line treatment received CTDa as second-line treatment and most who did not receive bortezomib as first-line treatment received it as second-line treatment.

- Costs were included for second-line treatment. The effect of second-line treatment on health outcomes was not included in the model because second-line treatments varied among the RCTs included in the Assessment Group's systematic review (see sections 4.1.8 and 4.1.16).
- Cost and outcomes of third-line and subsequent treatments were assumed to be the same between arms.
- People discontinued first-line treatment on disease progression.
- Health-related quality of life was better for those with complete response than those with less than complete response and was assumed to improve when people stop treatment.
- Adverse events were not modelled explicitly, but additional costs for treating the adverse events were included.

4.2.17 The base-case cost-effectiveness results were as follows:

- MPT compared with MP was associated with an ICER of £9174 per QALY gained based on an incremental effect of 1.22 QALYs and an incremental cost of £11,207.
- CTDa compared with MP was associated with an ICER of £33,216 per QALY gained based on an incremental effect of 0.26 QALYs and an incremental cost of £8592.
- VMP compared with MP was associated with an ICER of £29,837 per QALY gained based on an incremental effect of 1.20 QALYs and an incremental cost of £35,749.

4.2.18 The incremental cost-effectiveness analysis suggested that CTDa is extendedly dominated by MPT and MP, and that MPT

dominates VMP because it is more effective and cheaper. The incremental baseline cost-effectiveness results were as follows: CTDa compared with MP was associated with an ICER of £33,216 per QALY gained; and VMP compared with CTDa was associated with an ICER of £28,907 per QALY gained. The comparison of VMP versus MPT suggested that VMP and CTDa were unlikely to be cost-effective treatment options at the thresholds of £20,000 to £30,000 per QALY gained.

- 4.2.19 Sensitivity analyses showed the effects of a range of parameter values in the economic model. For each of the treatments the model results were most sensitive to the HRs for overall survival, cost and dosage of the treatment and the overall baseline survival curve used for MP. The deterministic sensitivity results for MPT versus MP varied between £6470 and £22,855 per QALY gained. The deterministic sensitivity analysis for VMP versus MP gave ICERs between £20,451 and £87,716 per QALY gained. VMP was dominated by MPT in all analyses apart from that investigating sensitivity to changes in overall survival. The deterministic sensitivity analysis for CTDa versus MP gave ICERs between -£29,388 (dominant, that is CTDa is more effective and less costly than MP) and £16,989 per QALY gained.
- 4.2.20 In addition to the sensitivity analyses, five alternative scenarios were explored to investigate the uncertainty around structural assumptions. In scenario A (no subsequent therapies), the ICERs for MPT, CTDa and VMP versus MP increased from £9174, £33,216 and £29,837, to £9738, £34,013 and £37,727 per QALY gained respectively.
- 4.2.21 Scenario B (vial sharing/fewer vials) investigated the cost effectiveness when patients share vials of bortezomib. With vial sharing and no wastage, the ICERs for MPT and CTDa versus MP increased from £9174 and £33,216 to £9369 and £33,492 per

QALY gained respectively. The ICER for VMP versus MP decreased from £29,837 to £22,549 per QALY gained. Following comments received from consultees on the draft assessment report, the Assessment Group undertook an additional scenario analysis in which it was assumed that four cycles or 31 vials of bortezomib were used, with no loss of efficacy. In this scenario, the ICER for VMP versus MP decreased from £29,837 (no vial sharing) to £18,996 per QALY gained. The ICER for VMP versus MPT decreased from -£1,000,000 (that is, MPT dominates VMP) to £319,923 per QALY gained.

- 4.2.22 Scenario C (inclusion of thalidomide maintenance trials) investigated the cost effectiveness using the estimate of efficacy for MPT from a meta-analysis that included trials with thalidomide maintenance. The manufacturer of bortezomib conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance. Using the HR from this analysis the ICER for MPT versus MP increased from £9174 to £24,390 per QALY gained. The ICERs for CTDa and VMP remained the same as in the base-case analysis (£33,216 and £29,837 per QALY gained respectively). In addition, MPT no longer dominated VMP, with an ICER of £32,739 for VMP versus MPT.
- 4.2.23 Scenario D (treatment effectiveness beyond the end of trial) investigated an alternative assumption whereby there is no treatment benefit for the three drug combinations over MP (that is, the event rates for these treatments are the same as for MP) after the end of the trial. This assumption had a large effect on the model results and all treatments were less cost effective than MP. The ICERs for each of the treatment options more than doubled to £20,698 (MPT), £71,264 (VMP) and £80,840 (CTDa) per QALY gained versus MP.

4.2.24 The probabilistic sensitivity analysis estimated the probability of each of the treatments being cost effective at the £20,000 and £30,000 thresholds. MPT had the highest probability (0.95 at both thresholds) of being cost effective. The baseline probabilistic sensitivity analysis showed that MPT was cost effective compared with MP, with an ICER of £9124. The comparisons of VMP versus MP and CTDa versus MP produced ICERs of £29,102 and £31,612 respectively.

Comparison of the manufacturer and Assessment Group models

4.2.25 The cost-effectiveness estimates differed between the manufacturers and the Assessment Group. This was a result of differences in incremental costs for MPT versus MP, differences in incremental QALY estimates for MPT versus MP (depending on whether trials with maintenance treatment were included), differences in the modelling of adverse events and inclusion of costs for second- and third-line treatments.

4.2.26 The incremental costs for MPT versus MP varied between £4888 (the manufacturer of bortezomib) and £19,768 (manufacturer of thalidomide). The manufacturer of thalidomide used higher dosages of thalidomide (238 mg/day) for longer periods (11 cycles) than the other two analyses. The incremental costs for VMP versus MP varied between £12,242 (manufacturer of bortezomib) and £41,251 (manufacturer of thalidomide). These differences were largely a result of the assumptions around the number of vials of bortezomib used, with the manufacturer of bortezomib assuming a mean of 31.5 vials per person, and the Assessment Group and manufacturer of thalidomide assuming over 40 vials. The incremental costs for CTDa versus MP varied between £2234 (manufacturer of bortezomib) and £8592 (Assessment Group). These differences were because of an error in the cost calculation for third-line therapy for CTDa by the

manufacturer of bortezomib.

- 4.2.27 The total QALY estimates used by the manufacturers and the Assessment Group were similar, with estimates for all treatment arms varying between 2.42 and 4.03. The incremental QALY estimates for MPT versus MP varied from 0.55 (manufacturer of bortezomib) to 1.22 (Assessment Group). These differences resulted from the estimates chosen for the HR for overall survival compared with MP. Estimates used by the manufacturer of bortezomib included studies with maintenance treatment whereas those used by the Assessment Group excluded studies with maintenance treatment.
- 4.2.28 There were differences in the way adverse events were modelled. The manufacturer of bortezomib included adverse events in the model as the cost of treating them. The manufacturer of thalidomide included adverse events in the model as a utility decrement at the time of the event and as the cost of treating them. The Assessment Group did not explicitly model adverse events for patient outcomes (that is, overall survival and progression-free survival), but included an additional cost for treating the adverse events in the model.
- 4.2.29 There were also differences in inclusion of costs after first-line treatment:
- The manufacturer of bortezomib included costs for second- and third-line treatments. Most people who received VMP as first-line treatment received CTDa as second-line treatment and most who did not receive VMP as first-line treatment received it as second-line.
 - The manufacturer of thalidomide assumed that patients discontinued first-line treatment on disease progression and did not include costs for second- and third-line treatments.

- The Assessment Group included costs for second-line treatments. Most people who received VMP as first-line treatment received CTDA as second-line treatment and most who did not receive bortezomib as first-line treatment received it as second-line.

Extra analyses post-consultation

4.2.30 Following consultation on the appraisal consultation document, the manufacturer of bortezomib submitted additional cost-effectiveness estimates using their model and applying different assumptions used by the Assessment Group, including evidence from studies including maintenance therapy, use of 31.5 vials of bortezomib and varying second-line therapies. The five scenarios were as follows:

- Scenario 1 investigated the use of 52 vials of bortezomib, with evidence of MPT efficacy from IFM 99/06 and IFM 01/01 studies and second-line therapies as in the Assessment Group model (see section 4.2.16).
- Scenario 2 investigated use of 52 vials of bortezomib, with evidence of MPT efficacy from a meta-analysis that included five trials with maintenance therapy, and second-line therapies as in the Assessment Group model (see section 4.2.16).
- Scenario 3 investigated use of 31.5 vials of bortezomib, with evidence of MPT efficacy from IFM 99/06 and IFM 01/01 studies and second-line therapies as in the Assessment Group model (see section 4.2.16).
- Scenario 4 investigated use of 31.5 vials of bortezomib, with evidence of MPT efficacy from a meta-analysis that included five trials with maintenance therapy, and second-line therapies as in the Assessment Group model (see section 4.2.16).
- Scenario 5 investigated use of 31.5 vials of bortezomib, with evidence of MPT efficacy from a meta-analysis that included five

trials with maintenance therapy, and second-line therapies as in the VISTA trial (see section 4.1.16).

- 4.2.31 For MPT versus MP, the ICERs for the five scenarios varied between £9138 (scenarios 1 and 3) and £17,337 (scenario 5) per QALY gained. The incremental costs varied between £8706 (scenarios 2 and 4), £9509 (scenario 5) and £12,104 (scenarios 1 and 3), and the incremental QALYs from 0.55 (scenarios 2, 4 and 5) to 1.32 (scenarios 1 and 3). That is, the QALY was reduced from 1.32 for those scenarios in which only two MPT studies (IFM 99/06 and IFM 01/01) were included to 0.55 when studies with maintenance therapy (5 studies) were included.
- 4.2.32 For VMP versus MP, the ICERs varied from £15,107 (scenarios 3 and 4) to £28,510 (scenarios 1 and 2) per QALY gained. The incremental costs varied from £17,615 (scenarios 3 and 4) to £33,244 (scenarios 1 and 2). The incremental QALYs for all scenarios were 1.17.
- 4.2.33 For VMP versus MPT, the ICERs varied between £14,426 (scenario 4), £21,565 (scenario 5) and £39,733 (scenario 2) per QALY gained. VMP was dominated by MPT in scenarios 1 and 3. The incremental costs varied from £5512 (scenario 3) to £24,538 (scenario 2) and the incremental QALYs varied from -0.16 (scenarios 1 and 3) to 0.62 (scenarios 2, 4 and 5).
- 4.2.34 The Assessment Group reviewed the additional scenarios presented by the manufacturer of bortezomib. It confirmed that there was close agreement between the two models when using the same assumptions and data for both models. However, the Assessment Group did not agree with the assumptions and the data used in the manufacturer's additional scenarios.

Extra analyses post-appeal

4.2.35 Following an Appeal Panel request, the Assessment Group's economic model, which had previously not been released because it contained confidential information, was released for consultation. Only the manufacturer of bortezomib (Janssen) submitted comments on the Assessment Group's economic model. The manufacturer of bortezomib incorporated a number of their proposed amendments to the Assessment Group's economic model and submitted revised cost-effectiveness estimates. These amendments related to the cost of managing adverse events, treatment duration of thalidomide based on mean duration observed in IFM99-06, IFM01-01 and VISTA trials, method for estimating QALYs, cost of second-line treatment and inclusion of three additional maintenance studies for thalidomide (GIMEMA, HOVON and NORDIC). The manufacturer of bortezomib presented three alternative scenarios for each of the comparisons (MPT versus MP, VMP versus MP and CTDa versus MP), in which the amendments were incorporated into the Assessment Group's economic model:

- Scenario 1 corrected for the cost of managing adverse events, treatment duration of thalidomide, QALYs estimated using Markov trace and cost of second-line treatment.
- Scenario 2 corrected for the inclusion of data from the pre-maintenance phase of maintenance studies (GIMEMA, HOVON, NORDIC) for the first 6-month period, in addition to the corrections listed in scenario 1.
- Scenario 3 corrected for the inclusion of data from the pre-maintenance phase of maintenance studies for the first 12-month period, in addition to the corrections listed in scenario 1.

4.2.36 For MPT versus MP the ICERs for the three scenarios varied from £11,511 (scenario 1) to £13,722 (scenario 3) per QALY gained.

For VMP versus MP the ICER was £19,505 per QALY gained for all three scenarios. For CTDa versus MP the ICERs varied between £11,890 (scenario 2) and £34,014 (scenario 1) per QALY gained. For VMP versus MPT, the ICERs varied between £36,794 (scenario 3) and £211,508 (scenario 1).

4.2.37 The Assessment Group commented on the proposed amendments and the revised cost-effectiveness estimates submitted by the manufacturer of bortezomib. The Assessment Group accepted that the model contained an error in the calculation of the adverse events costs, and that the use of a Markov trace may possibly provide a more accurate method for estimating the QALYs. The Assessment Group therefore provided revised cost-effectiveness results based on a revision to the adverse events costs and the use of a Markov trace to estimate the QALYs. The revised cost-effectiveness results were as follows:

- MPT compared with MP was associated with an ICER of £9189 per QALY gained based on an incremental effect of 1.21 QALYs and an incremental cost of £11,159.
- CTDa compared with MP was associated with an ICER of £33,703 per QALY gained based on an incremental effect of 0.25 QALYs and an incremental cost of £8544.
- VMP compared with MP was associated with an ICER of £29,930 per QALY gained based on an incremental effect of 1.19 QALYs and an incremental cost of £35,729.

The Assessment Group's incremental analysis showed that MPT continues to dominate VMP.

Summary of the cost effectiveness

4.2.38 The different assumptions and methodology used (see sections 4.2.25 to 4.2.37) resulted in a range of ICERs for the options for

first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. The Assessment Group and manufacturers' base-case cost-effectiveness results for MPT versus MP varied between £8912 (manufacturer of bortezomib) and £23,381 (manufacturer of thalidomide) per QALY gained. The Assessment Group and manufacturers' base-case cost-effectiveness results for VMP versus MP varied between £10,498 (manufacturer of bortezomib) and £29,837 (Assessment Group) per QALY gained. The Assessment Group and manufacturers' base-case cost-effectiveness results for CTDa versus MP varied between £10,905 (manufacturer of bortezomib) and £33,216 (Assessment Group) per QALY gained. The Assessment Group and manufacturers' base-case cost-effectiveness results for MPT versus VMP were £303,845 (manufacturer of thalidomide), and £319,923 (when the Assessment Group used the scenario of 31 vials of bortezomib) per QALY gained. The Assessment Group's incremental analysis of its base-case cost-effectiveness results suggested MPT dominates VMP because it is more effective and cheaper. The additional scenarios presented by the manufacturer of bortezomib following consultation on the appraisal consultation document (May 2010) resulted in ICERs for VMP versus MPT of £39,733 per QALY gained (scenario 2), £14,426 per QALY gained (scenario 4) and £21,565 (scenario 5). VMP was dominated by MPT in scenarios 1 and 3. The revised ICERs presented by the manufacturer of bortezomib and the Assessment Group following the release of the economic model for MPT versus MP varied between £9189 (Assessment Group) and £13,722 (manufacturer of bortezomib, scenario 3) per QALY gained, for VMP versus MP varied between £19,505 (manufacturer of bortezomib, all three scenarios) and £29,930 (Assessment Group) per QALY gained and for CTDa versus MP varied between £11,890 (manufacturer

of bortezomib, scenario 2) and £34,014 (manufacturer of bortezomib, scenario 1) per QALY gained. The Assessment Group's incremental analysis of its revised cost-effectiveness results suggested that MPT continued to dominate VMP.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bortezomib and thalidomide, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of bortezomib and thalidomide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee acknowledged the history of thalidomide as a teratogenic compound and noted that it is now prescribed and dispensed according to the Thalidomide Celgene Pregnancy Prevention Programme.
- 4.3.3 The Committee discussed the pathway of care for people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. The Committee heard from the clinical specialists that in UK clinical practice before the advent of thalidomide and bortezomib, first-line treatment consisted of an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid (attenuated dexamethasone or prednisolone). Since thalidomide and bortezomib had become available, one of these, according to patient preference, comorbidities and adverse events, was normally added to first-line treatment. The Committee heard from the clinical specialists and patient experts that although both the thalidomide and bortezomib regimens were well tolerated, administration of the bortezomib regimen took longer and was

less convenient than thalidomide (because it involved intravenous infusion rather than oral administration). The clinical specialists stated that a thalidomide regimen would be considered more appropriate for 70–75% of patients and that their preferred choice of regimen was thalidomide in combination with cyclophosphamide and attenuated dexamethasone (because of the mode of oral administration). The clinical specialists stated that they considered the two thalidomide regimens (CTDa and MPT), which both included an alkylating agent and a steroid, to be equivalent in terms of safety and efficacy. Past studies of the two regimens before the addition of thalidomide had shown equivalent safety and efficacy and the clinical specialists did not consider that the addition of thalidomide would have a differential effect. The Committee heard that for those people who were intolerant of thalidomide or had clotting disorders or impaired renal function, bortezomib in combination with melphalan and prednisolone was considered the most appropriate treatment. The Committee was not persuaded that comorbidities such as clotting disorders or renal impairment prevented a person from receiving thalidomide because they could be managed as outlined in the SPC for thalidomide. The Committee accepted that clinicians considered the three treatment regimens to be equivalent in terms of clinical efficacy, but that the choice of treatment for an individual patient will depend on the comorbidities present and the different mechanisms of action and adverse events associated with the treatments.

Clinical effectiveness

- 4.3.4 The Committee considered the estimates for the clinical effectiveness of MPT and CTDa. It noted that the Assessment Group had derived HRs for overall survival for thalidomide from two studies without maintenance treatment and had excluded studies in which participants received maintenance with

thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after first-line treatment with a combination regimen did not fall within the appraisal scope. It also noted that, if possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness. The Committee also heard from the clinical specialists and the manufacturer of thalidomide that not all participants in the maintenance studies benefited from maintenance treatment and that some people on thalidomide maintenance had a shorter overall survival, possibly because the prolonged thalidomide treatment induced disease resistance. The Committee concluded (see section 4.3.10) that to assign studies (published and ongoing) in which the results were confounded by treatment outside the appraisal scope equivalent weight to the two key studies without maintenance treatment was not justified. Nevertheless it was prepared to bear in mind these data without overemphasising them. Similarly the Committee considered the estimates of overall survival for CTDa and noted that the evidence came from preliminary results of the MMIX trial which included participants who had received maintenance treatment with thalidomide. The Committee noted these results but considered that the main conclusions on the clinical effectiveness of thalidomide should be derived from the MPT data. Based on these data, the Committee concluded that thalidomide in combination with an alkylating agent and a corticosteroid improved outcomes when compared with an alkylating agent and a corticosteroid in people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

4.3.5 The Committee discussed the relative effectiveness of bortezomib

in combination with an alkylating agent and a corticosteroid as presented by the Assessment Group. It noted that the evidence for the effectiveness of bortezomib in combination with an alkylating agent and a corticosteroid was derived from a single study (VISTA). This study showed that bortezomib was more effective than melphalan in combination with prednisolone in terms of overall survival and progression-free survival. It noted that survival rates with bortezomib were similar to those for thalidomide but that the two regimens were not compared head-to-head because of differences in participants' characteristics, delivery of the comparator and length of follow-up. The Committee concluded that it was likely that bortezomib in combination with an alkylating agent and corticosteroid improved outcomes to a similar degree to thalidomide in combination with an alkylating agent and corticosteroid.

Cost effectiveness

- 4.3.6 The Committee considered the base-case ICERs for thalidomide in combination with an alkylating agent and a corticosteroid from the Assessment Group's economic analyses. The Assessment Group calculated an ICER of £9170 per QALY gained for the MPT combination compared with MP and £33,200 per QALY gained for the CTDa combination compared with MP. The Committee accepted that if the safety and efficacy of the two thalidomide regimens were considered equivalent (see section 4.3.3), the ICER of £9170 for MPT was likely to be the more robust estimate because it was based on studies without thalidomide maintenance treatment.
- 4.3.7 The Committee also noted the variation in the ICERs presented by the manufacturers for MPT compared with MP (£8910 to £23,400). The highest of these, £23,400, was from the manufacturer of thalidomide and assumed higher dosages of

thalidomide and a greater number of cycles of treatment than the analyses from the manufacturer of bortezomib and the Assessment Group. The dosage of thalidomide used by the manufacturer of thalidomide was the maximum specified in the SPC but was higher than would be used in clinical practice (most patients are not able to tolerate such a high dose). The Committee considered that the ICER was likely to be lower than the estimate from the manufacturer of thalidomide and that the most plausible ICERs for the two thalidomide regimens would fall within the range considered a cost-effective use of NHS resources (below £20,000 to £30,000). The Committee therefore concluded that thalidomide in combination with an alkylating agent and a corticosteroid is a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

- 4.3.8 The Committee then considered the Assessment Group's ICERs for VMP compared with MP and with the thalidomide regimens. The Committee heard from the Assessment Group that the maximum dose of bortezomib specified in the SPC is eight cycles, which the manufacturer agreed would amount to 48 vials. The manufacturer of bortezomib stated, however, that on average only 31.5 vials were used in the VISTA trial. The manufacturer accounted for this difference on the grounds of dose reduction and dose delay. At the first Appraisal Committee meeting, the Committee accepted the concern raised by the manufacturer of bortezomib that the Assessment Group had assumed too many vials of bortezomib. Following consultation comments from the Assessment Group and on further discussion with both the manufacturer and the Assessment Group at the second meeting, the Committee considered that the costs of delayed doses might still reflect clinical practice and need to be considered. It therefore agreed that the manufacturer's preference for modelling 31.5 vials

should be considered the most optimistic estimate for clinical practice. The Committee noted that the Assessment Group's scenario that assumed four cycles (equivalent to 31 vials used) gave an ICER of £19,000 per QALY gained for VMP compared with MP and £320,000 per QALY gained for VMP compared with MPT.

- 4.3.9 The Committee noted the differences in the ICERs presented by the Assessment Group and the manufacturer of bortezomib for VMP compared with MPT. Apart from the fewer vials of bortezomib assumed by the manufacturer, the manufacturer of bortezomib also included costs for second-and third-line treatments in its model. This involved adding the cost of thalidomide to the bortezomib regimen, and of bortezomib to the thalidomide regimen, neutralising the approximately four-fold cost advantage of thalidomide, and greatly increasing the cost of MP. The Committee agreed that some accounting for second-line treatments was plausible, but not such that the cost of thalidomide in effect carried the cost of bortezomib, and certainly no more than the distribution of second-line treatments noted in the VISTA trial.
- 4.3.10 The Committee then considered the use by the manufacturer of bortezomib of a HR for overall survival for thalidomide which was derived from a meta-analysis that included RCTs with thalidomide maintenance. The Committee heard a strong case from the manufacturer of bortezomib that the maintenance studies should be included in the economic analysis, along with 31.5 vials and their estimate of the distribution of second-line treatments. The Committee was aware of the testimonies from the clinical specialists and the manufacturer of thalidomide (see section 4.3.4) that it was appropriate to exclude all the maintenance studies. However, the Committee took the view that it was

appropriate to consider the maintenance studies, but did not accept that results from these studies (which were confounded by treatment outside the appraisal scope) should be considered equivalent to the key studies without maintenance treatment. The Committee concluded that the most plausible ICER for bortezomib versus thalidomide could be less than the Assessment Group's base case of £320,000 per QALY gained, but would be considerably greater than those from the two most optimistic scenarios (£14,400, scenario 4 and £21,600, scenario 5) presented by the manufacturer of bortezomib (see section 4.2.30). The Committee therefore did not accept the manufacturer of bortezomib's assertion that the bortezomib regimen (VMP) was cost effective compared with the thalidomide regimen (MPT).

- 4.3.11 The Committee considered the revised cost-effectiveness estimates submitted by the manufacturer of bortezomib and the responses by the Assessment Group following release of the Assessment Group's economic model. It noted that the revised ICERs for MPT compared with MP presented by the Assessment Group and manufacturer of bortezomib were similar and slightly higher than their respective original base-case cost-effectiveness results (see sections 4.2.10 and 4.2.17). The Committee also discussed the revised ICERs for CTDa compared with MP presented by the Assessment Group and manufacturer of bortezomib. It noted that the Assessment Group's revised ICERs were similar and slightly higher to their base-case cost-effectiveness results, and the Committee reconfirmed its conclusion that the thalidomide evidence should be principally drawn from the MPT data. The Committee also noted that the revised ICERs presented by the manufacturer of bortezomib ranged from £11,900 to £34,000 and these were higher than its original base-case cost-effectiveness results (see sections 4.2.10 and 4.2.36). The Committee noted that the lowest estimate

(£11,900) included data from the maintenance studies which it had previously agreed should not be considered equivalent to the studies without maintenance treatment (see section 4.3.10). The Committee agreed that the manufacturer of bortezomib's revised ICERs for the two thalidomide regimens did not change the original decision that thalidomide in combination with an alkylating agent and a corticosteroid is a cost-effective option for the first-line treatment of multiple myeloma in people for who high-dose chemotherapy with stem cell transplantation is considered in appropriate. The Committee then discussed the revised cost-effectiveness estimates presented for VMP compared with MPT. It noted that the ICERs presented by the Assessment Group showed that MPT continued to dominate VMP and that the ICERs presented by the manufacturer of bortezomib exceeded £30,000 per QALY (£36,800 to £211,500 per QALY gained), despite the more optimistic estimate including the maintenance trial data. The Committee therefore concluded that these revised ICERs did not change their original assertion that VMP was not cost-effective compared with MPT.

- 4.3.12 However, the Committee did consider that bortezomib regimens could be cost effective for people who are unable to tolerate or have a contraindication to thalidomide. The Committee was aware that the contraindications specified in the SPC for thalidomide are pregnancy and hypersensitivity. It was mindful of the testimonies from the clinical specialists that people who are intolerant of thalidomide, or who had previous thrombosis or impaired renal function, are offered the bortezomib regimen (VMP). The Committee noted that comorbidities such as risk of thromboembolic events and renal impairment are highlighted in the posology section of the SPC for thalidomide, which describes that low molecular weight heparin or warfarin should be recommended in patients at risk of thromboembolic events, and

patients with renal or hepatic impairment should be monitored for adverse events. The Committee again considered the argument that the wording of the guidance around the contraindications to thalidomide should include people with comorbidities such as risk of thrombosis and impaired renal function. The Committee understood that thalidomide could be prescribed to people with renal impairment and risk of thromboembolic events if it is administered as outlined in section 4.2 (posology and method of administration) of the SPC for thalidomide. The Committee agreed that the SPC for thalidomide covered the safety risks adequately. The Committee concluded that since it had accepted the Assessment Group's ICER of £19,000 per QALY gained for VMP compared with MP (see section 4.3.8), bortezomib in combination with an alkylating agent and a corticosteroid is likely to be a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate and who are intolerant of or have contraindications to thalidomide.

- 4.3.13 In summary, the Committee considered that the combination of thalidomide plus an alkylating agent and steroid was both clinically effective and cost effective for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. The Committee considered that bortezomib plus an alkylating agent and steroid was not cost effective when compared with both thalidomide combinations, but was likely to be cost effective for the first-line treatment of multiple myeloma for people who are intolerant to or have contraindications to thalidomide.

Summary of Appraisal Committee's key conclusions

| TAXXX (MTA) | Appraisal title: Bortezomib and thalidomide for the first-line treatment of multiple myeloma | FAD section |
|---|---|-------------------|
| Key conclusion | | |
| <p>Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high dose chemotherapy with stem cell transplantation is considered inappropriate.</p> | | 1.1 |
| <p>Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:</p> <ul style="list-style-type: none"> • high-dose chemotherapy with stem cell transplantation is considered inappropriate and • the person is unable to tolerate or has contraindications to thalidomide. | | 1.2 |
| <p>The Committee concluded that thalidomide in combination with an alkylating agent and a corticosteroid improved outcomes when compared with an alkylating agent and a corticosteroid in people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.</p> | | 4.3.4 |
| <p>The Committee concluded that it was likely that bortezomib in combination with an alkylating agent and corticosteroid improved outcomes to a similar degree to thalidomide in combination with an alkylating agent and corticosteroid.</p> | | 4.3.5 |
| <p>The Committee concluded that thalidomide in combination with an alkylating agent and a corticosteroid is a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.</p> | | 4.3.7 |
| <p>The Committee did not accept the manufacturer of bortezomib's assertion that the bortezomib regimen (VMP) was cost effective compared with the thalidomide regimen (MPT). However, the Committee did consider that bortezomib regimens could be cost effective for people who are unable to tolerate or have a contraindication to thalidomide.</p> | | 4.3.11, 4.3.12 |
| Current practice | | |
| <p>Clinical need, including the availability of alternative treatments</p> | <p>Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy.</p> <p>The Committee discussed the pathway of care for people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. The Committee heard from the clinical specialists that in UK clinical practice before the advent of thalidomide and bortezomib, first-line treatment consisted of an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid (attenuated dexamethasone or prednisolone). Since thalidomide and bortezomib had become available, one of these, according to patient preference, comorbidities and adverse</p> | 2.3 4.3.3 |

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| | events, was normally added to first-line treatment. | |
| The technology | | |
| Proposed benefits of the technology | Thalidomide is an immunomodulatory agent. Its precise mechanism of action is under investigation and is currently unknown, but it is thought to have multiple actions, including anti-inflammatory activity and the ability to inhibit the growth and survival of myeloma cells and the growth of new blood vessels. It is also a non-barbiturate hypnotic sedative with central action. | 3.5 |
| How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | Bortezomib is an anticancer drug that works by reversible proteasome inhibition. This inhibition leads to arrest of the cell cycle and apoptosis (cell death), which reduces tumour growth. Myeloma cells are more sensitive to the action of bortezomib than normal cells. | 3.1 |
| What is the position of the treatment in the pathway of care for the condition? | The Committee heard from the clinical specialist that in UK clinical practice before the advent of thalidomide and bortezomib, first-line treatment consisted of an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid (attenuated dexamethasone or prednisolone). Since thalidomide and bortezomib had become available, one of these, according to patient preference, comorbidities and adverse events, was normally added to first-line treatment. The Committee accepted that clinicians considered the three treatment regimens to be equivalent in terms of clinical efficacy but that the choice of treatment for an individual patient will depend on the comorbidities present and the different mechanisms of action and adverse events associated with the treatments. | 4.3.3 |
| Adverse effects | Adverse events were not a key driver in the economic evaluation; however, see section 4.2.3, 4.2.8 and 4.2.16 for details of how adverse events were modelled by the manufacturers and the Assessment Group. | |
| Evidence for clinical effectiveness | | |
| Availability, nature and quality of evidence | The Committee noted that Assessment Group had derived hazard ratios for overall survival for thalidomide from two studies without maintenance treatment. The Committee accepted that it was appropriate for the Assessment Group to exclude from its analysis survival data from studies which included participants who had received maintenance therapy. | 4.3.4 |
| | The Committee noted that the evidence for the effectiveness of bortezomib in combination with an alkylating agent and a corticosteroid was derived from a single study (the VISTA trial). | 4.3.5 |
| Relevance to general clinical | Both thalidomide regimens and the bortezomib regimen are used in clinical practice for the first-line | 4.3.3 |

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| <p>practice in the NHS</p> | <p>treatment of multiple myeloma. The clinical specialists stated that a thalidomide regimen would be considered more appropriate for 70–75% of patients and that their preferred choice of regimen was thalidomide in combination with cyclophosphamide and attenuated dexamethasone (because of the mode of oral administration). They stated that they considered the two thalidomide regimens (CTDa and MPT) to be equivalent in terms of safety and efficacy. The Committee heard that for those people who were intolerant of or had contraindications to thalidomide, the bortezomib regimen (VMP) was considered the most appropriate treatment.</p> | |
| <p>Uncertainties generated by the evidence</p> | <p>The Committee was persuaded by advice from the clinical specialists that the two thalidomide regimens (CTDa and MPT), which both included an alkylating agent and a steroid, were equivalent in terms of safety and efficacy. The evidence for the clinical effectiveness of bortezomib in combination with an alkylating agent and a corticosteroid was derived from a single study (VISTA). The Committee noted survival rates with bortezomib were similar to those for thalidomide. However, the two regimens were not compared head to head. The Committee concluded that it was likely that bortezomib in combination with an alkylating agent and corticosteroid improved outcomes to a similar degree to thalidomide in combination with an alkylating agent and corticosteroid.</p> | <p>4.3.3 to 4.3.5</p> |
| <p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness</p> | <p>The Committee was mindful of the testimonies from the clinical specialists that people who are intolerant of thalidomide, or who had previous thrombosis or impaired renal function, are offered the bortezomib regimen (VMP). It noted that comorbidities such as risk of thromboembolic events and renal impairment are highlighted in the posology section of the SPC for thalidomide. It therefore concluded that bortezomib in combination with an alkylating agent and a corticosteroid is likely to be a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate and who are intolerant of or have contraindications to thalidomide.</p> | <p>4.3.12</p> |
| <p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p> | <p>The Committee concluded that thalidomide in combination with an alkylating agent and a corticosteroid improved outcomes when compared with an alkylating agent and a corticosteroid in people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.</p> <p>It noted that survival rates with bortezomib were similar to those for thalidomide but that the two</p> | <p>4.3.4 4.3.5</p> |

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| | regimens had not been compared head to head because there were differences in participants' characteristics, delivery of the comparator and length of follow-up. The Committee concluded that it was likely that bortezomib in combination with an alkylating agent and corticosteroid improved outcomes to a similar degree to thalidomide in combination with an alkylating agent and corticosteroid. | |
| Evidence for cost effectiveness | | |
| Availability and nature of evidence | The two manufacturers submitted cost-effectiveness models. The Assessment Group developed their own economic model and critiqued the economic models submitted by the manufacturers. | 4.2.1 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | <p>The Committee noted the variation in the ICERs presented by the manufacturers and the Assessment Group for MPT, CTDa and VMP compared with MP and MPT compared with VMP. The Committee accepted that the variation was a result of the following factors:</p> <ul style="list-style-type: none"> • Dosage and number of cycles of thalidomide • Number of vials of bortezomib • The inclusion of studies with thalidomide maintenance in the estimate of overall survival hazard ratio for thalidomide • costs for second-and third-line treatments. | <p>4.3.7</p> <p>4.3.8</p> <p>4.3.4,</p> <p>4.3.10</p> <p>4.3.9</p> |
| <p>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p> | No health-related benefits were identified that were not included in the economic models. | |
| Are there specific groups of people for whom the technology is particularly cost effective? | The Committee was mindful of the testimonies from the clinical specialists that people who are intolerant of thalidomide, or who had previous thrombosis or impaired renal function, are offered the bortezomib regimen (VMP). It noted that comorbidities such as risk of thromboembolic events and renal impairment are highlighted in the posology section of the SPC for thalidomide. It therefore concluded that bortezomib in combination with an alkylating agent and a corticosteroid is likely to be a cost-effective option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate and who are intolerant of or have contraindications to | 4.3.12 |

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| | thalidomide. | |
| What are the key drivers of cost effectiveness? | The key drivers of cost effectiveness of VMP compared with MPT were the inclusion of data from studies with maintenance treatment and the number of vials of bortezomib used. | |
| Most likely cost-effectiveness estimate (given as an ICER) | <p>The Committee considered the base-case ICERs for thalidomide in combination with an alkylating agent and a corticosteroid from the Assessment Group's economic analyses. The Assessment Group calculated an ICER of £9170 per QALY gained for the MPT combination compared with MP and £33,200 per QALY gained for the CTDA combination compared with MP. The Committee accepted that if the safety and efficacy of the two thalidomide regimens were considered equivalent (see section 4.3.3), the ICER of £9170 for MPT was likely to be the more robust estimate because it was based on studies without thalidomide maintenance treatment.</p> <p>The Committee agreed that the manufacturer's preference for modelling 31.5 vials should be considered the most optimistic estimate for clinical practice. The Committee noted that the Assessment Group's scenario that assumed four cycles (equivalent to 31 vials used) gave an ICER of £19,000 per QALY gained for VMP compared with MP and £320,000 per QALY gained for VMP compared with MPT.</p> | <p>4.3.6</p> <p>4.3.8</p> |
| Additional factors taken into account | | |
| Patient access schemes (PPRS) | Not applicable. | |
| End-of-life considerations | Not applicable. | |
| Equalities considerations | Not applicable. | |

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is

not required to fund treatments that are not recommended by NICE.

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

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

6 Related NICE guidance

Published

- Bortezomib monotherapy for relapsed multiple myeloma. NICE technology appraisal guidance 129 (2007). Available from www.nice.org.uk/guidance/TA129
- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. NICE technology appraisal guidance 171 (2009). Available from www.nice.org.uk/guidance/TA171

Under development

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

- Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma. NICE technology appraisal guidance (expected date of issue June 2012).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review by the Guidance Executive in July 2014. 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 C

May 2011

Appendix A: Appraisal Committee members and NICE project team

A *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 four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Dr Kathryn Abel

Reader and Consultant Psychiatrist / Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine / Anaesthesia Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay member

Dr Mary Cooke

Lecturer School of Nursing, Midwifery & Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Richard Devereaux-Phillips

Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Wasim Hanif MD FRCP

Consultant Physician & Honorary Senior Lecturer University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson

Professor of Primary Care Medicine, University of St Andrews

Professor Gary McVeigh

Cardiovascular Medicine, Queens University Belfast and Consultant Physician Belfast City Hospital

Dr Eugene Milne

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Ruth Oliver-Williams

Head of Nursing / Quality Improvement Lead Surgical Services, Royal Derby Hospital

Professor Katherine Payne

Professor of Health Economics, University of Manchester

Ellen Rule

Programme Director, NHS Bristol

Dr Danielle Preedy

Lay member

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens

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

Dr Matt Stevenson

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

Professor Paul Trueman

Professor of Health Economics, Brunel University, London

Dr Judith Wardle

Lay member

C ***NICE project team***

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

Sally Doss

Technical Lead

Nicola Hay

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Centre:

- Picot J, Cooper K, Bryant J, Clegg A et al. Bortezomib and thalidomide for the first-line treatment of multiple myeloma: a multiple technology appraisal (February 2010)

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, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Janssen
- Celgene

II Professional/specialist and patient/carer groups:

- Leukaemia CARE
- Macmillan Cancer Relief
- Myeloma UK
- British Society for Haematology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- UK Myeloma Forum

III Other consultees:

- Department of Health
- Hammersmith and Fulham PCT
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- GlaxoSmithKline
- Leukaemia Research Fund
- Medical Research Council Clinical Trials Unit
- Clinical Trials Research Unit (CTRU), University of Leeds
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Technology Assessment Centre, University of Southampton
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on Bortezomib and Thalidomide for the first-line treatment of multiple myeloma by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Gordon Cooke, nominated by UK Myeloma Forum – clinical specialist
- Dr Stephen Schey, nominated by NCRI/RCP/RCR/ACP/JCCO, Royal college of Physicians – clinical specialist
- Dr Kwee Yong, nominated by Royal College of Pathologists and BSH – clinical specialist
- Eric Low, nominated by Myeloma UK – patient expert
- Michael Brown, nominated by Myeloma UK – patient expert

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