Bortezomib monotherapy for relapsed multiple myeloma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Guidance

1.1 Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:

- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and

- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).

1.2 People currently receiving bortezomib monotherapy who do not meet the criteria in paragraph 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
2 The technology

2.1 Bortezomib (Velcade, Janssen-Cilag) is an anticancer drug that belongs to a novel class of drugs known as proteasome inhibitors. Bortezomib has a UK marketing authorisation as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation. For further information about the drug, see the summary of product characteristics (SPC).

2.2 Bortezomib treatment is associated with peripheral neuropathy, thrombocytopenia and other side effects. For full details of the side effects and contraindications, see the SPC.

2.3 The price of bortezomib is £762.38 for a 3.5-mg vial (excluding VAT; ‘British national formulary’, 53rd edition). The cost for one cycle of treatment would be approximately £3000. Costs may vary in different settings because of negotiated procurement discounts.
3 The manufacturer's submission

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

3.1 The manufacturer's submission approached the decision problem by comparing the clinical effectiveness of bortezomib with that of high-dose dexamethasone (HDD), based on the results of the APEX (Assessment of Proteasome Inhibition for Extending Remissions) randomised controlled trial (RCT). The population considered was people with multiple myeloma at first or subsequent relapse; however, the manufacturer's submission placed emphasis on patients at first relapse. The manufacturer considered HDD to be the most appropriate comparator because it is an effective monotherapy for relapsed multiple myeloma that is commonly used in clinical practice in the UK, and its use at first relapse is within its licensed indications. In addition, HDD was the comparator agreed as the basis for regulatory approval of the APEX RCT.

3.2 In an interim analysis of the APEX trial (median follow-up of 8.3 months), it was found that people receiving bortezomib had a statistically significantly longer median time to disease progression compared with people receiving HDD (6.2 months compared with 3.5 months, hazard ratio 0.55, 95% confidence interval 0.44 to 0.69; p < 0.001). They also had a significantly improved overall survival (hazard ratio 0.57, 95% confidence interval 0.40 to 0.81; p = 0.001) and a significantly higher overall (complete or partial) response rate (38% compared with 18%; p < 0.001). As a result of the interim analysis and the recommendation of the data monitoring committee, all patients in the dexamethasone group were offered bortezomib. Updated analyses were performed at 15.8 months and 22 months of follow-up. At 22 months follow-up, the median overall length of survival in the intention to treat population was 29.8 months in the bortezomib arm compared with 23.7 months in the HDD arm.

3.3 The manufacturer's submission provided cost-effectiveness evidence using a semi-Markov state-transition model to compare bortezomib with HDD. The manufacturer indicated that it did not include other comparators in the model because there is currently no UK consensus on best practice for the treatment of multiple myeloma at first relapse, because there are no other treatments available that hold a UK marketing authorisation for use at first relapse, and...
because of limitations in the available evidence. Because a high percentage of patients in the HDD arm of the APEX study were allowed to cross over to receive bortezomib, the manufacturer emphasised that the true difference in overall survival between the bortezomib and HDD arms was greater than in the reported results of the APEX study. Therefore, data from the Mayo Observational Study, which included some patients receiving a dexamethasone-containing regimen (a combination of vincristine, adriamycin and dexamethasone [VAD], of which dexamethasone is expected to be the most active ingredient), were used in addition to data from the APEX study in the modelling. The base case included people at first relapse only, resulting in a point estimate of the incremental cost-effectiveness ratio (ICER) of £31,000 per life year gained.

3.4 One-way sensitivity analyses of the key parameters identified in the manufacturer’s model resulted in a range of ICERs from £28,000 to £31,000 per life year gained and showed that the duration of treatment effect was the most influential parameter. Three scenario analyses were also presented.

- An analysis in which a rule was used by which patients whose disease had not responded to treatment (defined as not reaching complete or partial response using the European Blood and Marrow Transplant [EBMT] criteria) after three cycles would not continue treatment. Reductions in both bortezomib costs and survival benefit (resulting from discontinuing treatment) were included in the model. The reduction in survival benefit was calculated from the number of patients who responded within three cycles as a percentage of all those who responded.

- An analysis in which the proportion of patients entering the model at first and second or subsequent relapse was assessed.

- An analysis in which the use of bortezomib in combination with HDD was assessed.

3.5 In an additional analysis provided by the manufacturer in response to questions raised in the evidence-review phase, the base-case cost per life year gained of £31,000 was estimated to translate to £38,000 per quality-adjusted life year (QALY). The corresponding figure for a scenario with a three-cycle stopping rule with an ICER of £28,000 per life year gained was £33,500 per QALY gained. The QALYs were derived using utility values of 0.81 for the pre-progression state, and 0.64 after progression, based on a published study of patients with previously untreated multiple myeloma. The manufacturer requested that due
consideration be given to the view that it is more appropriate to measure cost effectiveness in terms of cost per life year gained in patients with multiple myeloma. The manufacturer argued that survival gain is the single most important outcome for people with relapsed multiple myeloma, that there is a lack of robust utility data to compute QALYs for people with relapsed multiple myeloma, and that the EuroQoL-5D (EQ-5D) quality of life (QoL) measure is not sensitive to some important facets of multiple myeloma.

3.6 The ERG raised a number of key issues about the manufacturer's submission.

- It raised concerns about the uncertainty in the cost-effectiveness analysis resulting from using data from the Mayo Observational Study. For example:
  - HDD was not one of the reported regimens for the observational study
  - the data used were a subset of the Mayo patient data
  - of the 335 participants in the Mayo study who had received one prior therapy and were on their second regimen, only 33 received a dexamethasone-containing regimen
  - the Mayo Observational Study reported data collected in the United States over a 13-year period, so patients may not have benefited from the latest treatment protocols
  - the observational data were not specific about which patients had what treatment and when
  - there were some differences between the patient profiles in the APEX RCT and the Mayo Observational Study; for example, patients in the APEX RCT were diagnosed approximately 5 years earlier than the Mayo patients
  - the data used may have predicted a more severe disease progression profile (that is, a shorter time to progression and higher mortality) than would be expected in a hypothetical cohort of patients treated with HDD in the context relevant for this appraisal.

- The model submitted by the manufacturer may have overestimated the true treatment effect of bortezomib because of the way in which data from the Mayo Observational Study were used to address the crossover in the APEX study.
• Adverse effects were not included in the economic model, in terms of either reduction in QoL or increased use of resources.

• The ERG's review of sensitivity analyses indicated a greater variability in cost-effectiveness estimates than was presented in the manufacturer's submission. The ERG found that the most influential parameters were the hazard ratio for time to disease progression and the cost of bortezomib.

• The ERG stated that, if patients are treated at a later stage of multiple myeloma, the cost per life year gained increases significantly. The ERG found that when all patients were treated at second relapse, the ICER was £77,000 per life year gained; when all patients were treated at third relapse, the ICER was £107,000 per life year gained.

3.7 The manufacturer's response to the issues raised included clarification on the APEX study and a revised economic report that included additional scenarios involving vial sharing. The costs of grade 3 or 4 adverse events were included, based on the frequency reported in the APEX RCT, resulting in an additional average cost of £1463 for bortezomib and £703 for HDD. There were four categories of adverse events: anaemia, thrombocytopenia, neutropenia, and all other grade 3 or 4 adverse events. The manufacturer also provided clarification about the impact of using data from the Mayo Observational Study, and stated that this affected only the modelling of post-progression survival and that the survival gain predicted by the model was realistic, or even conservative.

3.8 The manufacturer was further requested to provide details of a response-based rebate scheme that had been proposed to the Department of Health. In the manufacturer's proposed rebate scheme, the Velcade Response Scheme, 'responders' were defined as patients after first relapse whose disease reached at least a minimal response (measured as at least a 25% reduction in the first serum M protein response seen ['initial M protein']) after up to four cycles of bortezomib treatment. For people with myeloma who do not have measurable serum M protein levels (approximately 10 to 15% of patients) response would be assessed in terms of reduction in urinary free light-chain (Bence-Jones protein) excretion. The manufacturer also was asked to clarify the way in which the modelling of such a scheme differed from the model previously reviewed by the Committee. The manufacturer stated that the only difference in the modelling of costs between the stopping rule without rebate and with rebate is that the bortezomib drug costs are removed for non-responders up to the point at which they cease treatment. Additional costs to the NHS of administering the
scheme were not included. However, the manufacturer explained that these would be minimal because the rebate could be claimed using a simple form to be faxed to the manufacturer, and that the manufacturer would bear the cost of distributing replacement stock. As an alternative to replacement stock, the manufacturer would provide a credit note or cash refund.

3.9 The manufacturer provided the Committee with:

- Analyses based on a four-cycle stopping rule in addition to the three-cycle stopping rule originally proposed (see sections 3.4 and 3.5), with and without rebate for non-responders

- Analyses of response based on EBMT criteria as well as on the initial M protein response, with and without rebate for non-responders

- Analyses that had been adjusted to reflect the rebate of bortezomib costs that the manufacturer would pay to the NHS for those patients whose disease does not meet the required response criteria. This was in addition to the reduction in bortezomib costs and in survival benefit that had been used to calculate the ICER of £33,500 per QALY gained for a three-cycle stopping rule without rebate (see sections 3.4 and 3.5).

- Analyses in which minimal response was included in the definition of 'responder' used for the stopping rule and rebate scheme. This was in addition to the original analysis in which only complete and partial responders were defined as 'responders'. However, the manufacturer stated that because its model was based on time to progression and overall survival taken from the entire cohort in the bortezomib arm, the model did not allow separate estimation of these two outcomes for the minimal responder group. The manufacturer also stated that the minimal responder group of first-relapse patients in the APEX trial was too small to allow any meaningful analysis of time to progression and overall survival for this group alone. The model had not been constructed as a responder model, and specifically reflecting the expected health outcomes of minimal response patients would require a differently structured model.

3.10 The manufacturer provided data on the median time to progression separately for non-responders, complete responders, partial responders and minimal responders according to the levels of response at the fourth cycle of treatment. The details of this information were designated by the manufacturer to be commercial in confidence.
3.11 Data supplied by the manufacturer showed that, if no rebate scheme is applied, and EBMT criteria are used to assess response, the ICERs for bortezomib compared with HDD range from £33,500 per QALY gained for a three-cycle stopping rule for complete and partial responders only to £35,600 per QALY gained for a four-cycle stopping rule for complete, partial and minimal responders. If initial M protein is used to assess response and complete, partial and minimal responders are included, the ICERs for bortezomib compared with HDD range from £32,000 per QALY gained for a three-cycle stopping rule to £32,300 per QALY gained for a four-cycle stopping rule. The manufacturer did not provide ICERs for a scenario in which initial M protein is used to measure response and in which only complete and partial responders are included (as in the original modelling). These ICERs could be established from the manufacturer’s revised model, and were £26,500 and £29,000 per QALY gained for a three- and four-cycle stopping rule, respectively. However, the associated changes in cost and QALYs in the model showed that including minimal responders in the model resulted in higher costs but no further gain in QALYs.

3.12 Data supplied by the manufacturer showed that, if the manufacturer rebates the cost of treatment for patients whose disease does not meet the specified response criteria, and EBMT criteria are used to assess response, the ICERs for bortezomib compared with HDD ranged from £25,300 per QALY gained for a four-cycle stopping rule for complete and partial responders only to £28,100 per QALY gained for a three-cycle stopping rule for complete, partial and minimal responders. If initial M protein is used to assess response, the ICER for bortezomib compared with HDD ranged from £28,200 per QALY gained for a three-cycle stopping rule to £27,400 per QALY gained for a four-cycle stopping rule for complete, partial and minimal responders. The manufacturer did not provide ICERs for a scenario in which initial M protein is used to measure response and in which only complete and partial responders are included (as in the original modelling). However, these ICERs could be established from the manufacturer’s revised model. This showed ICERs of £20,700 and £20,900 per QALY gained for a four- and three-cycle stopping rule, respectively. The model showed that compared with the scenario resulting in an ICER of £20,700, all other scenarios resulted in higher costs but no further gain in QALYs.

3.13 Full details of all the evidence are in the manufacturer’s submission, the ERG report and the evaluation report.
4 Consideration of the evidence

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

4.2 The Committee discussed the position of bortezomib in the pathway of care for people with multiple myeloma. The Committee understood that the disease is incurable, and it was aware that because of the heterogeneous nature of the disease and its clinical course, the treatment appropriate for each patient at different times during the course of the disease may vary. The Committee understood that there are defined treatment pathways for relapsed multiple myeloma and that choice of therapy for an individual patient is influenced by the initial treatment and the response to it, the inherent characteristics of the disease and the patient’s performance status and preferences. The Committee recognised that many drugs used for the initial treatment of multiple myeloma have a limited evidence base for relapsed multiple myeloma and may also be costly. The Committee understood that bortezomib has a novel mechanism of action and that the APEX trial has established bortezomib as an evidence-based treatment for relapsed multiple myeloma. It concluded that bortezomib is considered a clinically important treatment for patients with multiple myeloma at both first and subsequent relapse.

Clinical effectiveness

4.3 The Committee considered the evidence for the clinical effectiveness of bortezomib monotherapy at both first and subsequent relapse. It understood that the only RCT that included patients at first relapse was the APEX study, which compared bortezomib with HDD. The Committee accepted that HDD was an appropriate comparator. It noted that the APEX study was the largest published RCT of the treatment of relapsed multiple myeloma, and that patients in the bortezomib arm experienced statistically significant improvements in time to disease progression and overall survival. The Committee also noted that ‘overall response’ was defined in the APEX trial as either complete or partial response and that patients in the bortezomib arm experienced statistically significant improvements in rates of overall response. The Committee
understood from the clinical specialists that there was a greater frequency of peripheral neuropathy and gastrointestinal adverse effects in the bortezomib arm, but that bortezomib was associated with less bone destruction and fewer infections than HDD. The Committee discussed the methods and results of the APEX study and considered the issues raised about the study in the ERG report. Taking all issues into account, the Committee concluded that the APEX study constitutes clear evidence that bortezomib monotherapy is more clinically effective than HDD monotherapy for the treatment of relapsed multiple myeloma.

4.4 The Committee discussed the alternatives to the use of bortezomib monotherapy for the treatment of relapsed multiple myeloma. It heard from clinical specialists that thalidomide is considered an important treatment for multiple myeloma and that it is currently being used without a UK marketing authorisation, both as first-line therapy and for relapsed multiple myeloma. The Committee also heard that bortezomib is likely to have enhanced effectiveness in combination with HDD and/or with cytotoxic drugs, and that a number of trials are either in progress or planned to investigate this. The Committee concluded that this additional research will be important to establish further the position of bortezomib in the pathway of care for multiple myeloma. However, because the current marketing authorisation for bortezomib is for its use as monotherapy, the Committee recognised that it was not in a position to make any recommendations about the use of bortezomib in combination with other drugs, including HDD.

Cost effectiveness without a response-based stopping rule

4.5 The Committee considered the cost effectiveness of bortezomib compared with HDD. The Committee understood that it was difficult to include other comparators in the model because of lack of evidence. However, it acknowledged that this contributed to the uncertainty in the assessment of cost effectiveness. The Committee discussed the base case and the sensitivity and scenario analyses of the manufacturer's economic model. It noted that clinical specialists have suggested several approaches for using bortezomib more cost effectively in the treatment of relapsed multiple myeloma, including its use at first relapse only. The Committee noted that the base case presented in the manufacturer's model, which included patients at first relapse only, resulted in an ICER of £31,000 per life year gained. It further noted from the ERG report
that treating patients at second relapse only or at third relapse only would result in markedly increased ICERs of £77,000 and £107,000 per life year gained, respectively. The Committee therefore accepted that bortezomib monotherapy is not cost effective when used at second or subsequent relapse.

4.6 The Committee discussed the manufacturer's view that it is more appropriate to consider cost per life year gained rather than cost per QALY as the measure of cost effectiveness in patients with multiple myeloma. The Committee did not accept this view (see section 3.5). It concluded that multiple myeloma and its treatments (including the adverse effects of treatment) would have significant effects on health-related QoL, that such effects are important to patients, and that sources of information to allow estimation of QALYs gained are available. The Committee noted that the additional analysis provided by the manufacturer at the request of the ERG, which estimated the impact of health-related QoL, resulted in a base-case ICER of approximately £38,000 per QALY. The Committee was concerned that the utilities assumed for patients with relapsed multiple myeloma may not accurately reflect the significant impairments in QoL that these patients can experience. Therefore, the Committee considered that the manufacturer's base-case ICER of approximately £38,000 per QALY for bortezomib compared with HDD was likely to be an underestimate.

4.7 The Committee considered the ERG's evaluation of the way in which survival was modelled in the manufacturer's submission. The Committee agreed that because of the degree of crossover that occurred between the arms of the APEX trial it was necessary and justified to adjust the APEX data. However, the Committee was concerned that there was uncertainty about the impact of using data from the Mayo Observational Study to make these adjustments in the model and that the modelling approach may have overestimated the effect of bortezomib treatment in the long term (see section 3.6). The Committee concurred with the ERG that the data used may predict a more severe disease progression profile than would be expected in a hypothetical cohort of patients treated with HDD at first relapse. It noted the manufacturer's assertion that the inclusion of the Mayo Observational Study data affected only post-progression survival. However, it did not agree with this view because the Mayo data had been used throughout the model and would therefore influence the modelling of both time to progression and overall survival for both bortezomib and HDD arms. Therefore, the Committee concluded that there was a high probability
that manufacturer’s base-case ICER for bortezomib compared with HDD was an underestimate.

4.8 The Committee discussed the scenario presented in the manufacturer’s response to the first appraisal consultation document issued for this technology appraisal in which vial sharing was proposed as a more cost-efficient use of bortezomib. The Committee was aware that the UK marketing authorisation for bortezomib specifies the single use of vials of bortezomib immediately after preparation. Additionally, the Committee expressed a number of concerns over the practice of vial sharing. These included issues related to maintenance of best aseptic practice and the practical constraints of patient numbers and geographical locations of myeloma centres. The latter would limit the possibility of several patients being treated in the same session over several cycles, each of which requires four doses of bortezomib at least 72 hours apart. The Committee was not persuaded that vial sharing could be considered either safe or routinely achievable in practice across the NHS.

Cost effectiveness with a response-based stopping rule

4.9 The Committee considered the scenario in the economic model in which patients whose disease had not responded after three cycles of bortezomib did not receive further treatment with the drug, whereas those who had achieved a partial or complete response received up to eight cycles of treatment. The Committee noted the adjustments required to the modelling, namely the reduction in bortezomib costs and in survival benefit that resulted from discontinuing treatment in people whose multiple myeloma had not responded after three cycles. The Committee heard from clinical specialists that the response to treatment can be assessed in an appropriate time frame to allow implementation of a stopping rule and that this approach is current practice in the UK. The Committee therefore accepted that such a stopping rule is feasible and that following this approach improves the cost effectiveness of bortezomib compared with a situation in which no such stopping rule is used. The Committee discussed the definition and evaluation of response, the number of treatment cycles used in the stopping rule, and the corresponding estimates of cost effectiveness.

4.10 The Committee discussed the method used to measure response to bortezomib treatment. It understood that the EBMT measurements used in the APEX RCT
were considered the 'gold standard' for definition of response. However, this full set of measurements is rarely used in clinical practice; instead, the measurement of serum M protein (which is a component of the EBMT measurements) is routinely used. The Committee heard from the clinical specialists that serum M protein is a specific marker for tumour load in an individual patient, so it is an appropriate measure of disease response in most patients. In addition, serum M protein showed a strong correlation with the full EBMT criteria used in the APEX RCT. The Committee appreciated that although changes in the concentration of serum M protein are a good measure of tumour response in an individual patient, they may not fully reflect the effect of treatment on overall life expectancy. The Committee also understood that 10–15% of patients do not have measurable serum M protein, in which case urinary free light chain (Bence Jones protein) is measured. The Committee accepted that for bortezomib to be used with a stopping rule, the appropriate measure for determining response would be serum M protein, except for those patients in whom M protein is not measurable and for whom a complete or partial response could be defined as a reduction of at least 90% in urinary free light chains.

4.11 The Committee discussed how a 'responder' should be defined if a stopping rule were implemented. The Committee noted that overall a response was defined in the APEX RCT as a reduction in serum M protein of 50% or more from baseline (that is, a complete or partial response). It also noted that the original modelling of a stopping rule was based on continuing treatment beyond three cycles in complete and partial responders only (see section 4.9). The Committee noted that the Velcade Response Scheme proposed by the manufacturer included an additional group of people whose disease demonstrated a minimal response (that is, a 25–49% reduction in serum M protein). The Committee heard from clinical specialists that a proportion of patients whose disease demonstrated an initial minimal response may go on to have a complete or partial response, so it would be desirable to continue treatment in minimal responders beyond three or four cycles. The Committee was concerned that minimal responders would not experience outcomes similar to complete or partial responders. The manufacturer provided the Committee with confidential time-to-progression data for minimal responders separately from non-responders and from complete and partial responders according to levels of response at the fourth cycle of treatment. The Committee considered that the variability in this
analysis was such that the true clinical outcomes experienced by minimal responders were uncertain.

4.12 The Committee discussed the number of cycles of treatment after which it would be appropriate to apply a stopping rule. The Committee understood that implementing a stopping rule after four rather than three cycles might reduce the proportion of people in whom treatment would be stopped but whose disease might otherwise have gone on to respond after further treatment. It therefore understood that clinicians and patients would value the option to continue treatment for up to four cycles. However, the Committee noted that the analysis in the manufacturer’s submission showed that no reduction in risk of progression was observed after three cycles. The Committee agreed in principle that it might be desirable that clinicians and patients have the option to continue bortezomib treatment for up to four cycles. However, it concluded that the number of cycles prior to a stopping rule would need to be determined by considering the incremental cost effectiveness of adding an additional treatment cycles beyond three cycles.

4.13 The Committee discussed the ICERs for the use of bortezomib at first relapse if a stopping rule were implemented. It noted that the ICER for bortezomib compared with HDD ranged from £32,000 to £35,600 per QALY. The Committee noted that moving from three to four cycles or adding the minimal responders increased the ICERs. However, when initial M protein – rather than EBMT criteria – was used as the method of assessing responders, the ICERs decreased. The Committee noted that the manufacturer did not provide ICERs for a scenario in which serum M protein was used and only complete and partial responders were included (as in the original modelling). However, it noted that these ICERs could be established from the manufacturer’s revised model and were in the range £26,500 to £29,000 per QALY gained for a three- and four-cycle stopping rule, respectively. The Committee was concerned that all these ICERs may be underestimates of the most plausible ICER. For the original analysis, the Committee was provided with additional confidential data by the manufacturer that estimated the ICER without adjustment for the crossover effect in the APEX trial. Although the Committee accepted that cross-over should be accounted for in the modelling, this analysis indicated the likely upper boundary in the cost effectiveness. The Committee considered the innovative nature of bortezomib and the severity of disease and the alternative treatment options for people at this stage of the disease. However, it concluded that, on
the basis of the evidence currently available, it was not in a position to recommend bortezomib without a rebate scheme.

**Cost effectiveness with response-based rebate scheme**

4.14 The Committee considered the scenario in which the manufacturer would rebate the cost of bortezomib for patients whose disease had not responded after a specified number cycles of bortezomib. The Committee noted the additional adjustment required to the modelling, namely the additional reduction in bortezomib costs achieved by the rebate. The Committee noted the concerns expressed by some consultees about the implementation of a rebate scheme, in particular that the administration of the scheme could be time and resource-intensive. It noted that the incremental cost to the NHS of implementing the scheme, including the staff time required to complete even a simple claim form, had not been included in the economic modelling. In considering these concerns, the Committee took account of the advice from the Department of Health that it considered that the scheme would not impose a disproportionate organisational burden on NHS organisations in England. The Committee took the view that the costs likely to be associated with the capture of the simple data needed to trigger an application to the manufacturer for a rebate, for the numbers of patients involved, would be substantially outweighed by the value of the rebate, and do not alter its conclusion on cost effectiveness.

4.15 The Committee noted that the most cost-effective approach to using bortezomib was to treat patients at first relapse, to measure serum M protein after four cycles, to discontinue and rebate treatment in people whose disease had responded less than partially, and to continue treatment only in those whose disease had responded at least partially. This approach resulted in an ICER of £20,700 per QALY. All other options, particularly the addition of continuing treatment in the minimal responder group (as in the manufacturer’s original Velcade Response scheme), carried a higher cost and no increase in QALYs. This implied that the incremental cost per QALY gained for the addition of the minimal responder group would be very high. The Committee reflected upon its overall concerns about the modelling methodology (see sections 4.6 and 4.7) and about the administration costs of the rebate scheme (see section 4.14). However, it agreed that, even if the ICER of £20,700 per QALY were an underestimate, it was likely that bortezomib monotherapy when given under
these circumstances would be a cost-effective use of NHS resources within the range that the Committee had previously accepted.
5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in ‘Standards for better health’ issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 ‘Healthcare Standards for Wales’ was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NHS organisations in England and Wales should operate the rebate scheme in accordance with the advice published jointly the manufacturer, the Department of Health and the Welsh Assembly Government alongside this guidance.

5.4 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 relapsed multiple myeloma and the doctor responsible for their care thinks that bortezomib monotherapy is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.5 NICE has developed tools to help organisations implement this guidance (listed below).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice.
6 Recommendations for further research

6.1 The Committee considered that further research into the effectiveness of bortezomib for the treatment of relapsed multiple myeloma is needed. Such studies should include:

- comparisons with other agents that are currently used in clinical practice in the NHS in England and Wales
- a robust design, adequate sample size and appropriate statistical analysis
- assessment of long-term prognosis, for which observational studies would be appropriate
- measurement of quality of life in patients with relapsed multiple myeloma, including the effect of treatment and adverse events
- a consideration of subgroups of patients in whom bortezomib might be particularly effective.

6.2 The Committee recommended that further research should be carried out to establish the survival benefit in patients treated with bortezomib at first relapse whose disease responds minimally (that is 25–49% reduction in serum M protein) and compare this with that in complete and partial responders.
7 Related NICE guidance

7.1 There is no related guidance for this technology.
8 **Review of guidance**

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed.

8.2 A review was proposed in March 2012. For details, see the [NICE website](https://www.nice.org.uk/). In line with usual practice, NICE will consult with the manufacturer, other consultees and commentators to ensure that the timing of the review of this appraisal takes account of the developing evidence base on this drug.

Andrew Dillon  
Chief Executive  
October 2007
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

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

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

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

Professor Keith Abrams (2006–2007)
Professor of Medical Statistics, University of Leicester

Dr Jeff Aronson (2006–2007)
Reader in Clinical Pharmacology, Radcliffe Infirmary

Dr Darren Ashcroft (2006–2007)
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair) (2006–2007)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry (2006–2007)
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan (2006–2007)
Director of the Health Economics Facility, University of Birmingham
Mr Brian Buckley (2006)
Vice Chairman, InContact

Professor John Cairns (2006–2007)
Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Mike Campbell (2006)
Statistician, University of Sheffield

Dr Mark Chakravarty (2006–2007)
Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK)

Dr Peter I Clark (2006–2007)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology NHS Trust, Merseyside

Dr Mike Davies (2006)
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips (2006)
Public Affairs Manager, Medtronic

Professor Jack Dowie (2006–2007)
Health Economist, London School of Hygiene and Tropical Medicine

Ms Lynn Field (2006–2007)
Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler (2006–2007)
Professor of Surgical Education, University of London

Dr Fergus Gleeson (2006–2007)
Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch (2006–2007)
Former Director of Nursing and Workforce Development, Mid Essex Hospital Services NHS Trust
Mrs Barbara Greggains (2006–2007)
Lay member

Mr Sanjay Gupta (2006–2007)
Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Professor Philip Home (2006–2007)
Professor of Diabetes Medicine, University of Newcastle

Dr Peter Jackson (2006)
Clinical Pharmacologist, University of Sheffield

Professor Peter Jones (2006)
Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Dr Mike Laker (2006)
Medical Director, Newcastle Hospitals NHS Trust

Dr George Levy (2006)
Lay member

Ms Rachel Lewis (2006)
Nurse Advisor to the Department of Health

Mr Terence Lewis (2006–2007)
Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh (2006–2007)
Professor of Cardiovascular Medicine, Queens University, Belfast

Professor Jonathan Michaels (2006)
Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne (2006–2007)
Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology Assessment, University of Southampton
Dr Neil Milner (2006–2007)
General Medical Practitioner, Sheffield

Dr Rubin Minhas (2006–2007)
General Practitioner and CHD Clinical Lead, Medway PCT

Dr John Pounsford (2006–2007)
Consultant Physician, North Bristol NHS Trust

Dr Rosalind Ramsay (2006–2007)
Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Christa Roberts (2006–2007)
UK Country Manager, Abbott Vascular

Dr Stephen Saltissi (2006–2007)
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott (2006)
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Mark Sculpher (2006–2007)
Professor of Health Economics, University of York

Dr Lindsay Smith (2006–2007)
General Practitioner, East Somerset Research Consortium

Mr Roderick Smith (2006–2007)
Finance Director, Adur, Arun and Worthing PCT

Mr Cliff Snelling (2006–2007)
Lay member

Dr Ken Stein (2006–2007)
Senior Lecturer in Public Health, Peninsula Medical School, University of Exeter

Professor Andrew Stevens (2006–2007)
Professor of Public Health, University of Birmingham
Dr Rod Taylor (2006–2007)
Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth.

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

Helen Chung
Technical Lead

Elisabeth George
Technical Adviser

Reetan Patel
Project Manager
Appendix B: Sources of evidence considered by the Committee

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


B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on bortezomib monotherapy for relapsed multiple myeloma by providing a written statement to the Committee. Organisations listed in I and II had the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Janssen-Cilag

II) Professional/specialist and patient/carer groups:

- Cancerbackup
- International Myeloma Foundation (UK)
- Leukaemia Care Society
- Long-Term Medical Conditions Alliance
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Palliative Care
- Tenovus Cancer Information Centre
- Association of Cancer Physicians
- Association of Surgeons of Great Britain and Ireland
British Association of Surgical Oncology

British Oncological Association

British Oncology Pharmacy Association (BOPA)

British Psychosocial Oncology Society

British Society for Haematology

Cancer Research UK

Community Practitioners' and Health Visitors' Association

Royal College of General Practitioners

Royal College of Nursing

Royal College of Pathologists

Royal College of Physicians of Edinburgh

Royal College of Physicians' Medical Oncology Joint Special Committee

Royal College of Radiologists

Royal College of Surgeons

Royal Pharmaceutical Society

UK Myeloma Forum

Department of Health

Sedgefield PCT

Southend PCT

Welsh Assembly Government

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

Board of Community Health Councils in Wales

British National Formulary
• Medicines and Healthcare products Regulatory Agency (MHRA)
• National Public Health Service for Wales
• National Coordinating Centre for Health Technology Assessment (NCCHTA)
• NHS Confederation
• NHS Purchasing and Supplies Agency
• NHS Quality Improvement Scotland
• Baxter Healthcare (cyclophosphamide)
• Bristol-Myers Squibb Pharmaceuticals (carmustine)
• Clonmel Healthcare (vincristine)
• GlaxoSmithKline (melphalan)
• Mayne Pharma (doxorubicin, vincristine)
• Medac (UK) (doxorubicin)
• Pfizer (cyclophosphamide, doxorubicin)
• Pharmion (thalidomide)
• Schering-Plough (interferon alfa-2b)
• Teva Pharmaceuticals (doxorubicin)
• National Collaborating Centre for Cancer
• Institute of Cancer Research
• Haemato-oncology Department, King’s College Hospital
• Leukaemia Research Fund
• MRC Clinical Trials Unit
• National Cancer Research Institute
• Scottish Medicine Consortium
C. The following individuals were selected from clinical specialist and patient advocate nominations from non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on bortezomib for the treatment of multiple myeloma by providing written or oral evidence to the Committee. They were also invited to comment on the ACD.

- Professor Gareth Morgan, Professor of Haematology and Head of Clinical Unit, nominated by the International Myeloma Foundation and the Institute of Cancer Research – clinical specialist

- Dr Graham Jackson, Consultant Haematologist, nominated by the British Committee for Standards in Haematology – clinical specialist

- Dr Stephen A Schey, Chair, UK Myeloma Forum – clinical specialist (present at the Appraisal Committee meeting on behalf of Dr Graham Jackson, who was unable to attend)

- Mr Brian Jago, nominated by the International Myeloma Foundation – patient expert

- Mr Eric Low, Chief Executive, International Myeloma Foundation (UK) – patient expert

- Dr Jamie Cavenagh, Consultant Haematologist nominated by the British Society for Haematology – clinical specialist (present at FAD meeting)
Changes after publication

March 2014: implementation section updated to clarify that bortezomib monotherapy is recommended as an option for treating relapsed multiple myeloma. Additional minor maintenance update also carried out.

March 2012: minor maintenance
About this guidance

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

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

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

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

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