NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Bortezomib treatment of relapsed and refractory multiple myeloma

Response to consultee and commentator on the Appraisal Consultation Document (ACD)

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Janssen-Cilag	**As requested we have structured our comments using the headings suggested in your letter dated 17th July.** WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST-EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE We believe that three areas of concern drove the Appraisal Committee's provisional recommendation: 1. A perceived lack of clarity around the role of bortezomib in the multiple myeloma (MM) treatment pathway. 2. A concern around the clarity and detail in the reporting of the APEX trial. 3. Concerns with the economic model, resulting in the conclusion that bortezomib "had not been shown to be cost-effective compared with clinical practice in the NHS". We provide comments on each of these three specific issues below. ***THE APPRAISAL COMMITTEE INDICATE A PERCEIVED LACK OF CLARITY AROUND THE ROLE OF BORTEZOMIB IN THE MULTIPLE MYELOMA TREATMENT PATHWAY.*** *We contend however that Bortezomib is clearly established as the evidence-based standard of care for patients at 1st relapse* 1.1 The Appraisal Committee is incorrect in stating that treatment pathways for multiple myeloma (MM) are poorly defined. Treatment pathways do exist and are clearly documented in clinical guidelines. Most notable from a UK context are the 2005 guidelines developed by the British Committee on Standards in Haematology (Smith et al 2005, updated with Morgan et al 2005), which is a subgroup of the British Society for Haematology. This committee recommends that Bortezomib is available for clinicians to use in accordance with its licence, ie in patients with relapsed myeloma. Although guidelines are helpful, MM is a heterogeneous and incurable disease and therefore patients need access to different treatment options at different times during the course of their disease. We would recommend therefore that the Appraisal Committee carefully consider the unique characteristics of MM and its treatment and that it actively works to understand these complex issues through dialogue with relevant professional bodies such as the UKMF, BCSH and Royal College of Pathologists.	The Appraisal Committee considered the position of bortezomib in the pathway of care and this is discussed in section 4.2 of the FAD.

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	1.2 Bortezomib represents a significant advance in the treatment of MM and is the only new licensed treatment for this disease in over a decade. It is also the only agent specifically licensed for relapsed myeloma. The unprecedented data seen in the phase II SUMMIT and CREST trials, confirmed in the phase III APEX trial, are due to bortezomib's unique mechanism of action, that of intra-cellular proteasome inhibition. This is a fundamentally different mechanism from current chemotherapy options, hence bortezomib is also active in patients who have resistance to previous therapy. The proteasome is fundamental to the survival of myeloma cells, thus, bortezomib's targeted effect on the proteasome translates into significant clinical efficacy by directly inducing cell death.	The Appraisal Committee considered the evidence for the clinical effectiveness of bortezomib monotherapy and this is discussed in section 4.3 of the FAD.
	1.3 Section 1.1 of the ACD suggests that there is a need for additional trials to establish the position of bortezomib in the pathway of care for people with MM. We strongly disagree with this statement and believe that there is certainty around where bortezomib should be used in the MM treatment pathway. This is because the APEX trial (Richardson et al, 2005), established bortezomib as the evidence-based standard of care for patients with relapsed MM. The APEX trial is the largest, peer-reviewed RCT ever to have been published in patients with relapsed MM. This means that bortezomib is supported by level one evidence from an RCT that the ERG rates as being of "reasonable quality" when judged against standard NICE quality criteria. The APEX trial confirmed that bortezomib improved response rates and increased time to progression and survival compared to high dose dexamethasone (HDD) in patients with MM at first relapse and beyond. This result demonstrated that bortezomib is a highly effective treatment in relapsed myeloma relative to the only other treatment (HDD) licensed for use in this population.	The Appraisal Committee considered the position of bortezomib in the pathway of care and this is discussed in section 4.2 of the FAD. The Appraisal Committee considered ongoing and future research of bortezomib in multiple myeloma and this is discussed in sections 4.10, 4.11 and 6.1 of the FAD.
	1.4 The APEX trial also precisely clarifies bortezomib's place in the treatment pathway. When data were analysed according to whether patients received treatment at 1st relapse compared to second relapse and beyond, (Sonneveld et al, 2005), results show that the patients treated at 1st relapse had increased time to progression, survival and higher response rates. This clearly shows that there is greater benefit derived from bortezomib for patients at 1st relapse rather than later in the treatment pathway, and provides NICE with clear evidence on how to ensure that bortezomib is used most effectively in the NHS. A consensus has also emerged within the clinical community on this issue. As previously mentioned, the BCSH who aim to provide haematologists with evidence based guidelines using a well-defined development process, support the use of bortezomib at 1st relapse on the basis of the APEX study (Morgan et al, 2005). Most recently, another recognised government sponsored guideline development group, Cancer Care Ontario (http://www.cancercare.on.ca) have recommended bortezomib as the preferred treatment option for relapsed MM: *"For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option*" (Reece et al, 2006).	The Appraisal Committee considered the use of bortezomib in patients at first relapse compared with second or subsequent relapse, as discussed in section 4.5 of the FAD.
	1.5 The addition of dexamethasone to bortezomib in patients with relapsed and/or refractory myeloma, who had suboptimal responses to bortezomib alone, was associated with improvement in responses without prohibitive toxicity. In the CREST study in particular, where patients presented after failing only one prior treatment regimen, a	The Appraisal Committee considered the use of bortezomib in combination with

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	12% increase in overall response was seen with the addition of dexamethasone (Jagannath et al 2004). These findings represent clinical validation of the additional benefit from the combination of bortezomib with dexamethasone, as demonstrated in preclinical models (Hideshima et al, 2001). The use of combination therapy is a well-established principle in the treatment of cancer, hence addition of dexamethasone to enhance response rates with bortezomib is not unexpected, and has been shown to be effective and well tolerated as evidenced by its inclusion in section 5.1 of the SmPC for Velcade (bortezomib). Consequently the addition of HDD to bortezomib monotherapy is now established as routine by many clinicians in the UK.	dexamethasone, and this is discussed in section 4.8 of the FAD.
	1.6 Ortho Biotech notes that the ACD appears contradictory on the issue of licence status. The ACD whilst acknowledging that thalidomide, a treatment that has no marketing authorisation in the UK, is commonly used in clinical practice, it is however also suggested that it [thalidomide] could have been a comparator in this appraisal. The committee however fails to emphasise its [thalidomide's] unlicensed status and the consequences of this for undertaking such a comparator study. Conversely the committee fails to accept the appropriateness of combining two licensed treatments (bortezomib and dexamethasone) in a manner acknowledged within bortezomib's SmPC and which has been proven to be an effective strategy in clinical trials.	Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6 and sections 4.9 and 4.10.
	1.7 The ACD suggests that the lack of standardisation [of treatment pathways] means that clinical trials are required that focus on the establishment of the position of bortezomib in the pathway of care. Bortezomib is however the now established evidence-based standard of care in patients at 1st relapse and we therefore argue that the purpose of this single technology appraisal process is to evaluate whether bortezomib is a clinically and cost-effective use of NHS resources. Detailed consideration of treatment pathways are more appropriate for NICE to consider within the clinical guideline process.	For the purposes of this appraisal, it was important for the Committee to establish the position of bortezomib in the treatment pathway in order to appraise the clinical and cost effectiveness of bortezomib in the various scenarios presented in the manufacturer's submission. Such appraisal includes consideration of the clinical appropriateness of any subgroups or scenarios considered and the relevant comparators in each scenario.

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	High dose dexamethasone is the only appropriate comparator for bortezomib in this appraisal	
	1.8 To provide further clarity around the place of bortezomib in the treatment of relapsed MM, it is also important to consider the choice of comparator in this appraisal as highlighted in section 4.3 of the ACD. As stated in paragraph 1.1, by necessity, treatment of relapsed MM needs to be individualised and patients will need access to a range of treatments throughout the course of their illness. Therefore, we believe that it is appropriate for a range of therapies, including bortezomib, to be made available if the treatment goals of achieving durable response and improved survival are to be achieved. As patients inevitably relapse, they will require access to a range of different agents during their myeloma treatment journey. Alternative treatments used in relapsed MM include repeat stem cell transplant, alkylating agents and thalidomide. It is clear from section 4.3 of the ACD that the committee particularly note that thalidomide is an agent commonly used at first relapse. Given the importance of this statement to the constitution of the draft guidance, we will address this point in some detail below, however at this point iterate two important aspects of thalidomide which have not been sufficiently considered by the committee; These are; 1. We emphasise again that thalidomide is unlicenced and therefore we are unable to conduct a comparative study as suggested by the committee. 2. Within the UK there is an increasing use of thalidomide for first line or first line maintenance treatment such that in relapsed myeloma, thalidomide is no longer a treatment option. The reasons for choosing HDD as the comparator arm in the APEX study thus becomes apparent though are dealt with later in this response.	The Appraisal Committee noted the difficulties in providing a comparison with thalidomide, as stated in the Manufacturer's Submission. Amendments have been made in the FAD, see sections 4.2, 4.7 and 4.10.
	1.9. We endorse the ERG conclusion that there are no obvious comparators other than HDD for this appraisal. However, section 4.3 of the ACD states that the committee felt that *"….lack of standardisation in the current management of MM should not preclude efforts to establish the clinical and cost-effectiveness of bortezomib within the spectrum of options used in current practice in the NHS.."* We would like the Appraisal Committee to appreciate that other treatment options were only excluded after due consideration and for sound methodological and clinical reasons. We are pleased to have the opportunity to clarify this point in the following sections. However it is important to realise that HDD is a vital component of many other treatment regimens in myeloma, eg VAD, a gold standard regimen for intensive treatment in newly diagnosed myeloma patients. Indeed the principle active component of this regimen is in fact the dexamethasone.	The Appraisal Committee was aware of the difficulties in considering potential comparators other than HDD in the model, but noted that the exclusion of such other comparators lead to additional uncertainty in the overall results. See FAD sections 4.2 and 4.7.
	1.10 In the absence of comparative RCT data, it is sometimes possible to make indirect comparisons between treatments using techniques such as meta-analysis, although the validity of this approach is somewhat open to question. Also, before it can even be attempted, it is important that the internal validity and similarity of the trials being compared is carefully examined and that the findings are interpreted cautiously (Jones et al 2004). With this in mind, we iterate why HDD is the only relevant comparator below.	Comment noted.
	1.11 Thalidomide is commonly used in the treatment of relapsed MM. However, robust and meaningful comparisons of efficacy, safety and cost-effectiveness with bortezomib are not possible. We would argue that the safety, effectiveness and cost-effectiveness of thalidomide remain uncertain because the manufacturer of this product has failed to invest in proper phase III development plans. This means that thalidomide has no marketing authorisation and is not currently approved by the MHRA for any indication in the UK. In fact, there are no randomised, controlled trials evaluating thalidomide in patients with relapsed MM (Glasmacher et al, 2005).	Amendments have been made in the FAD, see sections 4.2 and 4.10.

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	Unsurprisingly given this dearth of RCT data, the optimal dosing schedule for this product remains to be established. The limitations with the thalidomide evidence base means that indirect comparisons are simply not possible. Given all these facts, it is also obvious why thalidomide could not have been chosen as a comparator in our phase III APEX study.	
	1.12 If NICE were to fail to recommend the use of bortezomib, it means that patients with relapsed MM would be denied the option of using a product proven to work in this patient population in a robust RCT, but would be free to continue using an unlicensed product with efficacy unproven in adequately designed trials in this patient group. Furthermore, thalidomide is not a cheap generic treatment. Maintenance treatment acquisition costs of 50mg to 400mg doses are around £5,000 and £20,000 per year. NICE aims to deliver guidance to ensure that there is appropriate use of scarce NHS resources and yet the guidance in its current form would actually condemn NHS resources to be diverted towards a product that fails to meet any kind of modern, evidence-based medicine criteria. Perversely, NICE would be rewarding a lack of innovation and R&D investment on the part of the manufacturers of thalidomide by removing bortezomib as an option for patients.	Comments noted.
	1.13 The ACD drew attention to various other alternative treatment options and raised the suggestion that repeat stem cell transplant and anti-cancer chemotherapy are alternative treatment options. The effectiveness of repeat stem cell transplants in relapsed disease is unproven such that it would be considered to be an experimental procedure at this stage. At present this expensive procedure is rarely offered a second time in the UK and its value is currently being addressed in the context of clinical trials. Although some patients are re-exposed to previously used anti-cancer drugs such as alkylating agents, this is not a worthwhile option for many patients. Novel licensed treatment options such as bortezomib therefore fulfil an unmet medical need.	Amendments have been made in the FAD, see sections 4.2 and 4.10.
	A concern around the clarity and detail in the reporting of the APEX trial	
	2.1 The ACD (section 3.5) raises concerns around the APEX trial stating that *"lack of clarity and detail in reporting the APEX RCT made the interpretation of clinical effectiveness difficult*". Ortho Biotech is concerned that in this instance, the ACD lacks balance by failing to include the ERG's final conclusion that "**these limitations do not significantly affect the overall results especially in light of clarifications received from the manufacturer."** We concur with the ERG that the APEX results are robust and that concerns over reporting of the trial were dealt with in our response to questions raised by the ERG. However, in the following sections, we provide some further information on the rationale for choosing HDD as the comparator in the APEX study, and also to clarify any remaining issues relating to the reporting and analysis of APEX.	The Appraisal Consultation Document states that the Committee concluded that bortezomib has shown clinical benefits compared with HDD. The considerations of clinical evidence for bortezomib monotherapy are discussed in section 4.3 of the FAD.
	2.2 HDD is commonly used for relapsed myeloma in clinical practice in both North America and Europe and it is considered to be an effective treatment in this setting. In the absence of an established optimal treatment for relapsed myeloma, the rationale for the selection of the comparator to VELCADE in the APEX study was based on:	Comments noted.

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	Treatments available at the time the APEX study commenced (June 2002) ***The treatment considered effective in clinical practice*** ***The treatment most widely used in North America and Europe*** HDD met these criteria and hence was considered by the investigators, the sponsor, the FDA and the European Regulatory Authorities to be the most appropriate comparator for the APEX study. 2.3 The ERG highlighted some apparent discrepancies between the information included in our submission and other sources such as the Richardson paper. We have fully investigated all possible discrepancies and are confident that there are no major issues that would impact the interpretation of the APEX trial. Our full set of responses to these issues are provided in Appendix 1. ***CONCERNS WITH THE ECONOMIC MODEL, RESULTING IN THE CONCLUSION THAT BORTEZOMIB "HAD NOT BEEN SHOWN TO BE COST-EFFECTIVE COMPARED WITH CLINICAL PRACTICE IN THE NHS".*** 3.1 The ERG critique of our economic model was largely fair and balanced and we note their conclusion that ***"in general the approach taken to model disease progression and cost-effectiveness in this patient group seems reasonable".*** However, we question why this important comment, which brings a more balanced perspective to the critique, was omitted from the ACD. 3.2 We are mindful of the need to address the ERG's concerns in order to provide the Appraisal Committee with an economic evaluation that is fit for purpose. To address this, we have fully updated our original economic model and a detailed, revised report is provided in Appendix 2 of this document. The key elements that have been updated from our original submission include: a full QALY-based cost-effectiveness analysis; a detailed response to specific comments raised within the ERG report and a revised set of results incorporating all changes that were proposed as being necessary by the ERG. The key elements of this revised report are highlighted below. 3.3 In revising the economic model, we have used a two-stage approach to ensure the impact of the changes we have made are as transparent as possible. In the report in Appendix 2, we have also carefully responded to all the ERG comments and made changes to the model as appropriate. Ortho Biotech would be happy to meet with the NICE team to explain our approach in more detail if that would be helpful.	Comment noted. Comment noted. The Appraisal Consultation Document is not intended to be a comprehensive summary of underlying evidence, but rather highlights key areas of the evidence base which relate to the Appraisal Committee's decisions. Comments noted. See sections 3.6, 4.6 and 4.7 of the FAD. Comments noted.

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In the first set of analyses, we provide a full QALY-based analysis using the original submitted model and calculated results for the following scenarios

1st Relapse: An analysis of patients treated at 1st relapse
1st Relapse plus stopping rule: Limiting the number of cycles of bortezomib in non-responding patients

1st Relapse combination treatment: The combination of bortezomib plus dexamethasone versus HDD

1st Relapse combination plus stopping rule: The combination of bortezomib + dexamethasone and limiting the number of cycles of bortezomib in non-responding patients.

The table below presents a summary of the cost-effectiveness results for the different scenarios, with more detailed information available in Appendix 2.

Patient Group	Cost per QALY	95% CI
First relapse	£38,052	£33,629-£48,612
First relapse + stopping rule	£34,964	£30,314-£47,105
Bortezomib + Dex	£35,410	£33,293-£48,026
Bortezomib+ Dex + stopping rule	£31,764	£29,354-£47,437

The results show that

the incremental cost per QALY becomes more favourable when bortezomib is used with the stopping rule and in combination with dexamethasone. When these two strategies are employed, the cost per QALY is around £30,000.

3.5. Before presenting the results of the revised economic model, it is important to respond to the comments raised by the ERG and to describe actions we have taken to address these issues. This is described in some detail in Appendix 2. Of particular note are ERG concerns around the use of the Mayo Clinic cohort in our model (the Kumar observational study).

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	3.6. We agree with the ERG that Kumar is a good quality observational study and that it is the only published, credible long-term cohort data available for modelling progression in MM. The ERG state that TTP is one of the two most important drivers of cost-effectiveness in the model (cost of bortezomib being the other). It is very important to understand that the TTP and 1-year survival rates for both Bortezomib and HDD were taken directly from the randomised phase of APEX and we are therefore highly confident that these are accurate and robust parameters to use in modelling the effectiveness of HDD and bortezomib. The model is therefore driven by the APEX RCT, and the Kumar data are only used to predict post progression survival, with the same assumptions applied to both arms of the model. As a result, Kumar is not a key driver of the model.	This is discussed in sections 3.3 and 4.7 of the FAD.
	3.7. Another key concern of the ERG was the apparent lack of HDD in the Kumar study. In fact, this is not a limitation of the model because the Kumar data are only used to model post progression survival. By definition, patients in the HDD arm would therefore have failed HDD treatment and would need to receive alternative treatments. In the model, parameter estimates of the effectiveness of HDD are taken directly from APEX.	This is discussed in section 4.7 of the FAD.
	3.8 The final major concern was whether the model overestimates survival relative to the APEX results from the Richardson et al paper. Having examined this issue, we are confident that this is not the case and that the modelled survival of 9.9 months is realistic, or even conservative. The figure below presents overall survival results at 22 months follow-up of the APEX trial (as presented by Paul Richardson at the American Society of Haematology conference in December 2005). In this analysis, the incremental survival gain for bortezomib was 6 months. However, it is important to note that in Richardson's analysis, 62% of patients (208 patients) in the HDD arm had crossed over to receive bortezomib when the study was halted prematurely on ethical grounds because of the superior benefits seen in the bortezomib arm. Therefore, the figure below is not a balanced comparison of bortezomib and HDD. Instead, it should be considered to be a comparison of bortezomib versus "HDD followed by bortezomib". To illustrate this point, the dashed line on the graph below shows the approximate rate of decline during the randomised phase. This is much steeper that the decline after the trial was halted and patients in the HDD arm were allowed to receive bortezomib. In fact, it shows exactly why it is necessary to construct a model to show the true extent of the treatment differences. It is more than reasonable for the model to predict that had patients in the HDD arm not been allowed to receive bortezomib treatment at the point of early trial termination, then the difference between bortezomib and HDD would have been greater than 6 months. Given the superior TTP and response rates observed with bortezomib, we believe that 9.9 months is likely to be a realistic, or even conservative estimate.	This is discussed in sections 3.6 and 4.7 of the FAD.

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	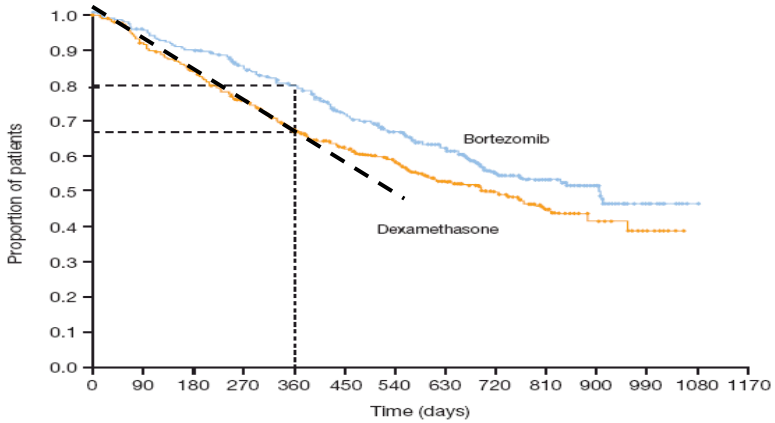 3.9 The revised economic model is an update of the original work provided in the manufacturer's submission. We have implemented the following improvements to our model in direct response to the ERG critique: • We have implemented a revised analysis incorporating a more systematic approach to utility valuation in the model. We now use the utility value from the van Agthoven study (0.81) for patients in pre-progression and a value of 0.644 in post progression. This latter figure was based on the lower utility value reported by the ERG in Section 6.3.4.3, p36 of their report. • The model cycle length is now 3-monthly for the entire time horizon of the model • Costs of adverse events are now fully included, based on frequency and severity seen in APEX • Cost of administration of bortezomib have been updated in line with ERG comments. • We have revised sensitivity analysis ranges to use those suggested by ERG. • We have considered a scenario that includes vial sharing as suggested by ERG. Market research shows that around 15% of vials are currently shared in the UK. A summary of the updated cost-effectiveness results are presented in the table below. **Patient Group** / **Cost per QALY** / **95% CI** First relapse / £38,064 / £33,236- £47,381 First relapse + stopping rule / £33,515 / £28,518 – £44,135 First relapse + Bortezomib + Dex / £35,059 / £33,964-£47,540 First relapse + Bortezomib + Dex + stopping rule / £30,586 / £28,678-£43,717 First relapse + stopping rule + vial sharing / £30,112 / £25,924 - £39,913	This is discussed in sections 3.6, 4.6 and 4.7 of the FAD.

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First relapse + bortezomib + dex + stopping rule + vial sharing	£27,566	£22,141 - £39,215

There are a number of key conclusions that can be drawn from this new set of analyses.

1. When bortezomib is used at 1st relapse and treatment is stopped in non-responders after three cycles, the incremental cost per QALY is £33,500 which is in the range that one would consider to be cost-effective.

   This is discussed in sections 4.6 and 4.7 of the FAD.

2. Addition of dexamethsone together with a stopping rule is the most cost-effective strategy for using bortezomib, with a cost per QALY of £30,500.

   This is discussed in section 4.9 of the FAD.

3. An analysis reflecting current UK patterns of vial sharing suggests that the cost per QALY with stopping rules is around £30,000. Addition of dexamethasone to this scenario gives a cost per QALY of £27,500.

   This is discussed in section 4.8 of the FAD.

4. Given that this is a rapid, early STA, which is based on a single trial, it is our assertion that the 95% CIs give a degree of assurance that this technology is likely to be a cost-effective use of resources. None of the scenarios have upper limits that are a very large factor above the threshold and the point estimates are consistently around £30,000. Under the new STA process, which requires decision-making on the basis of early, more limited data we would argue that tighter PSA intervals are not achievable.

   Comment noted.

WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

4.1 In the preceding sections, we addressed issues relating to the appraisal of evidence in this submission. In addition, we would like to comment on the ACD's proposal that bortezomib should be restricted for use in *"well-designed clinical studies that focus on the establishment of the position of bortezomib in the pathway of care for people with multiple myeloma in comparison with other agents that are currently used in clinical practice in England and Wales"*. Ortho Biotech believes that this proposed recommendation is inappropriate for a number of reasons.

Amendments have been made in the FAD; see sections 1.1, 4.2, 4.10, 4.11 and 6.1.

4.2. Firstly, as stated above, the position of bortezomib in the pathway of care was clarified in 2005 by the APEX study and therefore, further studies are not needed to establish where bortezomib can be used most effectively.

This is discussed in sections 4.2 and 4.3 of the FAD.

4.3 Secondly, it could be that NICE believes that the on-going MRC myeloma IX study will answer the question as to where bortezomib should be positioned, however this is not the case. Bortezomib plus dexamethasone was added to the study as an optional amendment and because it is a proven, valuable treatment for first relapse MM patients. Furthermore in this study, allocation to bortezomib treatment is not random, which is likely to limit the relevance of this study to a HTA. The study is not intended to assess either the efficacy or position of bortezomib as these questions have already been answered in the APEX trial.

This is discussed in sections 4.2, 4.9 and 4.11 of the FAD.

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	SUMMARY 5.1 In conclusion, the APEX trial established bortezomib as the evidence-based standard of care for patients with relapsed MM and in doing so, clarified its appropriate place in the treatment pathway. The ACD recommendation to use bortezomib only in clinical trials is therefore not appropriate. APEX has already successfully answered this question. 5.2. Bortezomib patients had superior response rates, increased time to progression and survival compared to HDD and the benefits were most pronounced in patients who received it at first relapse. Our revised economic analysis confirms that bortezomib is most cost-effective when used at 1st relapse and when treatment is limited to three cycles in non-responders. Combination with dexamethasone further enhances response rates and cost-effectiveness. 5.3 Ortho Biotech believes that the available evidence supports guidance recommending the use of bortezomib as a treatment option for appropriate patients at first relapse. Appropriateness can be judged by individual clinicians, but at least should include an assessment of performance status. Implementation of a stopping rule and consideration of co-administration with dexamethasone can help ensure that bortezomib treatment is a cost-effective use of scarce NHS resources. **References** Glasmacher et al. A systematic review of phase II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. British Journal of Haematology 2005; 132: 584-593 Hideshima, T et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Research 2001; 61: 3071-3076 Jagannath, S et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. British Journal of Haematology, 2004; 127: 165-72. Jones L et al. Using the adjusted indirect comparison in a Health Technology Assessment (HTA): clopidogrel versus modified-release dipyridamole. http://www.cochrane.org/colloquia/abstracts/ottawa/P-122.htm Morgan, G et al. Position statement on the use of bortezomib in multiple myeloma. 2005. http://www.bcshguidelines.com/pdf/Bortezomib_250705.pdf Reece et al. Bortezomib in Multiple Myeloma and Lymphoma: A Clinical Practice Guideline. http://www.cancercare.on.ca/pdf/pebc6-18s.pdf	This is discussed in FAD sections 1.1, 4.2, 4.3 and 4.11. This is discussed in FAD sections 1.1, 4.2, 4.3 and 4.11. This is discussed in FAD sections 4.4 to 4.9.

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	Richardson et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. New Engl J Med 2005; 352: 2487-2498 Sonneveld P et al. Bortezomib at first relapse is superior to high-dose dexamethasone and more effective than when given later in relapsed multiple myeloma. Poster Presentation 10th International Myeloma Workshop, April 10th – 14th 2005, Sydney, Australia. For details of Appendix 1: Clarification of Issues Related to the APEX study, and Appendix 2: Revised Economic Report, can be accessed at http://www.nice.org.uk	The comments on the Evidence Review Group Report were brought to the attention of the ERG and the Appraisal Committee.
Nominated patient experts and clinical specialists		
Patient Expert	**1** In respect of relevant evidence being taken into account, yes,in general terms it would appear that all the relevant evidence has been taken into account **2** In respect of clinical and cost effectiveness and impact on the NHS, sadly I cannot agree. It may well be that the clinical summary is a reasonable interpretation of the evidence submitted, but when one considers cost effectiveness I feel that the issue has been totally clouded by the fact that the NHS is in a perceived current financial crisis. The evidence considered document concludes that the position of Bortezomib in the clinical pathway for people with Multiple Myeloma is uncertain at present ,but as a patient who received a 5 cycle course of Bortezomib in Jan 2006 which has now placed me in remission, it seems, in my experience, the pathway is extremely clear. My conclusion is that decisions made may have a fiscal background. **3**.In respect of sound recommendations for guidance for the NHS I cannot agree that the provisional recommendations form an appropriate response to a drug that has been shown in my case to improve the quality and duration of life. My personal view of this document is that money is more important than a patient's life, and this cannot be a sound basis for recommendation.	Comment noted. The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness. Any new treatments recommended should be cost effective compared with existing treatments.
Clinical specialist 1and The Institute of Cancer Research	Thank you for giving me the opportunity to reply to the ACD for the Velcade submission. I had the opportunity to comment during the panel meeting and the opportunity to explain the clinical setting for Velcade treatment in myeloma was very welcome. Given the rules under which the appraisal was conducted, I found the conclusions appropriate. The definitive conclusions were that: i) '***Velcade is an effective treatment for myeloma and that is clearly superior to Dexamethasone and the data supporting this is greater than for any other treatment for myeloma'.*** *ii)* ***The cost per QALY is less than £30,000'*****,** which falls within an acceptable range.	In the base case (patients at first relapse, monotherapy, no stopping rule), the cost per life year gained was estimated in the manufacturer's submission

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		to be £31,000 (see Manufacturer's Submission section 3.7.3, page 84), the corresponding cost per QALY was estimated to be £38,000 (see Evidence Review Group Report, p.64).
	While I agree with these conclusions, the further interpretation of this is much more difficult to accept.	
	The ACD states that Velcade should only be available as part of a clinical trial. This effectively makes it impossible for patients with myeloma to receive this treatment and will undoubtedly impact in a very unfavourable fashion on the survival for these patents. There is currently no clinical trial, which is open for recruitment other than Myeloma IX, which is due to close in the near future. While conceptually it is correct to try to stimulate entry into clinical trials, in the absence of any such trials, which are currently running and the long time period involved in setting up such trials, together with the lack of compulsion on individual Trusts to support the financial cost of trial drugs, the advice is currently inappropriate. In addition, there is a well-described syndrome of PCTs not wishing to prescribe Velcade unless it is in a clinical trial. If it is in a clinical trial, they do not want to fund it because it is research and the companies should fund it.	Amendments have been made in the FAD; see sections 1.1, 4.10, 4.11 and 6.1.
	I would like to make a number of specific points:	
	i) Even at <£30,000 per QALY, the cost per QALY looks artificially high, not least because of the low cost Dexamethasone, but because it was not possible for the committee to consider the use of Velcade outside its licensed setting; this is inappropriate. It is very clear that the number of responses and outcomes are better when Velcade is combined with Dexamethasone, and if no response occurs within 3 cycles, it is possible to discontinue treatment. This decreases the cost per QALY further. A simple combination with oral alkylating agents such as Cyclophosphamide together with Dexamethasone can increase the response rates even further, and opens the possibility of longer disease free survival after cessation of treatment. This approach is clearly how the drug will be used in practice and a number of trials are currently looking at combinations such as this for presenting patients. There is a very sensible clinical rationale for making these simple combinations that has been worked out over the last 40 years of chemotherapy use. The response rate with combinations is very high, and patient's survival can be very long indeed. It is inappropriate to artificially set the rules such that this type of information cannot be accepted. There is a clear danger that with the pace of ongoing studies and with a large study of MP Velcade near to completion, that the NICE advice will seem ridiculously out of date.	Comments noted. In the base case (patients at first relapse, monotherapy, no stopping rule), the cost per life year gained was estimated in the manufacturer's submission to be £31,000 (see Manufacturer's Submission section 3.7.3, page 84); the corresponding cost per QALY was estimated to be £38,000 (see Evidence Review Group Report, p.64). Amendments have been made in the FAD, see sections 4.4, 4.6 to 4.9 and 4.12. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the

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		Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6
	ii) The treatment policy for first and second relapse of myeloma is actually clear and laid out in the BCSH guidelines: a. For older patients who may have received Melphalan and Prednisolone at presentation it would be appropriate to try the same treatment again if they have relapsed years after the initial exposure. If they failed to respond MP at presentation or relapsed early after first exposure, the use of Velcade would be highly appropriate. b. For younger patients autologous transplantation is the initial treatment of choice. If patients relapse early then Velcade may be appropriate. For patients who relapse after 18 months, a repeat autologous transplant, or Velcade would be appropriate. The cost comparison in this setting is very favourable.	Amendments have been made to the FAD, see section 4.2.
	iii) For patients with relapsed myeloma attaining a response is essential. Failure to obtain a response is followed by a rapid progression to death. Thus in selecting the treatment for relapse there are a number of considerations. If a patient has been exposed to a drug before, they are likely to be resistant to it on subsequent exposure. The drug should be tolerable with few side effects, and give good responses. Any drug that gives a good response is likely to be effective clinically. Thus from a clinical perspective, randomised comparisons are perhaps not as relevant as may be thought to be in some quarters. We simply need to know what the prior treatment was, the performance status of the patient, the rate of responses, and duration of responses after they have been treated.	Amendments have been made to the FAD, see section 4.2.
	iv) It was implied in the meeting that although Dexamethasone was used in the Velcade trials, a more appropriate comparison was with Thalidomide. It is very difficult to consider Thalidomide as a comparator treatment for relapse. Much as the rules are set for the consideration of Velcade as a single agent, so they should be set for the consideration of Thalidomide. Thalidomide is highly effective at relapse, and is moving more into the first line setting, and it is likely most people will receive Thalidomide as part of the first line or maintenance treatment in the future. However, Thalidomide is not a licensed drug, and to consider it in the context of the ACD seems, therefore, inappropriate.	Amendments have been made to the FAD, see sections 4.2, 4.7 and 4.10.
	v) Conceptually stimulating entry into clinical trials is highly appropriate, especially for expensive novel agents. To state unequivocally though that Velcade can only be available for patients in clinical trials is highly inappropriate. As the Principle Investigator of the only trial that is using Velcade at relapse in the UK, it is important to say that the trial was not designed to address the question of how to use Velcade. However, that study will give further insight into the use of Velcade, how it should be sequenced, and the impact of prior treatments. It is not, however, a formal relapse trial. The study, Myeloma IX is due to close and no new	Amendments have been made in the FAD, see sections 1.1 and 4.11.

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	patients will be able to be recruited into it within 6 to 12 months. As the median survival in the study is approaching 54 months, it will continue to recruit in the relapse setting. Patients who have not been entered into the study will not be eligible for treatment with Velcade. The ACD advice is also ethically inappropriate even if a trial at relapse was set up, because of the necessity for equipoise in the trial design, any study would have to be an early versus late Velcade study. This is because it has clearly been demonstrated that Velcade is effective therapy at relapse. I felt that the appraisal was fair, and the results clear. That is that Velcade at relapse as a single agent is a more effective treatment than Dexamethasone as a single agent. The data supporting this conclusion is greater than it is for any other treatment at relapse. However, I feel the interpretation of this data is incorrect. There is clearly a place for Velcade in the treatment and relapsed and refractory myeloma. This does not have to be exclusively in the clinical trial setting. I applaud the Committee's desire to strengthen clinical trial entry. However, I feel that in the setting of myeloma, it is highly inappropriate as it effectively means that patients in the UK will be denied a highly effective treatment, which can induce responses where they would not otherwise be obtained, and can thus prevent death from myeloma occurring. Trials should be developed to evaluate this drug for relapsed myeloma in the UK, however, these would take a minimum of 2-3 years to set up and even then, Trusts and PCTs may not support the additional drug costs. My suggestion would be that Velcade was approved for relapsed myeloma and its use directed by the BCSH position statement on it. Appropriate trials should be initiated now. It should be recommended that Velcade is used in simple combinations and if responses are not attained, then it is appropriate to stop treatment.	Amendments have been made in the FAD, see sections 1.1, 4.2, 4.3, 4.10, 4.11 and 6.1. The Appraisal Committee considered the use of bortezomib in combination with dexamethasone and other drugs, and this is discussed in sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6. The Appraisal Committee considered the clinical and cost effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD.

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Clinical Specialist 2 and Royal College of Pathologists and British Society of Haematology	We write as the representatives of the Haematology community through the Royal college of Pathologists and the British society of Haematology. Haematologists organise the overall care of myeloma patients in the UK and organise the many facets of the care of this complicated disease. We would like to formally express our disappointment with the preliminary recommendations for the use of Bortezomib in multiple myeloma in England and Wales as summarised in the recent appraisal consultation document. There has been a large response to this document from the Haematology community and the overwhelming (100%) response has been disappointment and concern. The arguments we will present are very similar to those that will be presented by the UKMF and the patient representatives and this reflects the broad agreement between physicians, other health care professionals and patient groups that the findings in the appraisal document are disappointing and will deprive patients facing a very difficult malignant process of one of the most effective agents in the treatment of this disease – indeed there is no evidence that there is another treatment as effective as Velcade in the relapse setting. In answer to the formal questions 1. We do not feel any major evidence has been taken into account but the whole context of myeloma care has not been fully considered. 2. We do not consider the clinical and cost effectiveness summaries are reasonable interpretations of the evidence – see below. 3. We do not consider the provisional recommendations of the appraisal committee to be sound – see below We wish to put before the committee a number of arguments which we wish to be taken into consideration during this period of further consultation. • Myeloma is currently an incurable disease, extremely variable in its biological basis and clinical expression, and that the aim of all treatments at the present time is to improve the quality and duration of life. The management approach to this disease is different to other haematological and non-haematological malignancies, where cure is the goal, and can be achieved with currently available therapy. • There is no strong evidence base on which to approach the treatment of relapsed/ refractory myeloma. There are however clearly defined treatment pathways for myeloma and over the course of the disease patients will receive different combinations of treatment at different times. Myeloma care is well organised however and follows well established and up-dated guidelines. • Until the publication of the Apex trial there was no robust, large, prospective randomised controlled trial to inform the decisions clinicians made at the point of relapse and it was appropriate that physicians chose the therapy which best matched the patients need. Initial treatment and patient's response to it, the inherent characteristics of the disease, patient's performance status and patient preferences all influence treatment choice. With the publication of the Apex trial physicians do now have evidence on which to base the treatment	Comments noted. Amendments have been made to the FAD, see sections 4.2 and 4.3. Comments noted. The Appraisal Committee understood the incurable nature of multiple myeloma and its variability in biological basis and clinical expression. Amendments have been made to the FAD, see section 4.2. Amendments have been made in the FAD see sections 4.2, 4.3, 4.4 and 4.5.

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	decision at relapse. We believe that the position of Bortezomib in the pathway of care has now been established and that it should, in the group of patients we will define below, be the agent of choice for the treatment of first relapse.	
	• We note the Appraisal committee's recommendation that the position of Bortezomib is uncertain and that it should be established more clearly by the results of on going research, however we assert that further trials are unnecessary because the Apex trial data has unequivocally demonstrated the efficacy of Bortezomib. Indeed any further trials performed in relapsed patients would be unethical unless Velcade was chosen as the control arm i.e. the established best therapy against which other therapies could be compared. • Such trials would not be supported by funding bodies nor would clinicians have enthusiasm for them as they see that the role of Bortezomib as monotherapy has been established. They are now interested in the question of how Bortezomib performs in combination with other drugs. Finally it is also very difficult to believe that in the current financial climate of the NHS such a trial would be funded by Trusts and PCTs.	Amendments have been made in the FAD, see sections 4.3, 4.10, 4.11 and 6.1.
	• We wish to endorse the choice of High Dose Dexamethasone (HDD) as a suitable comparator. Often used in combination with other cytotoxic agents (e.g.VAD, CVAD, ZDEX etc) both for initial treatment, and at relapse, studies have shown that HDD alone is almost as effective as the combinations and is the most powerful component of the combinations. This knowledge has lead to its widespread use as a single agent worldwide.	The Appraisal Committee agreed that HDD is an appropriate comparator; see section 4.2 of the FAD.
	• That Bortezomib is more effective than High Dose Dexamethasone is highly significant. We feel it represents a major advance for patients who have commonly had both cytotoxic chemotherapy and recently also Thalidomide, as initial treatment. For these chemo- resistant patients the fact that Velcade acts by an entirely different mechanism is highly significant	Amendments have been made in the FAD, see section 4.2.
	• Further, on the question of the validity of HDD as the choice of comparator we believe it is important to be aware that 70% of patients with myeloma now receive a Thalidomide containing regime as initial treatment which markedly limits its use as an alternative comparator to Velcade at relapse. We believe that acknowledging the use of HDD as a valid comparator in this setting is important not only for this trial but also for future trials of new agents.	The Appraisal Committee agreed that HDD is an appropriate comparator, and understood the difficulties in making comparisons with alternative treatments. However, the Appraisal Committee considered that the lack of information regarding the comparison of bortezomib with alternative treatments lead to additional uncertainty in the overall results, see FAD sections 4.2, 4.10 and 4.7.

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	• We note that the appraisal committee concluded that Bortezomib had not been shown to be cost effective compared with current practice in England and Wales. However we believe that insufficient account has been taken of the following points which materially affect this conclusion. We believe that physicians can and will stop therapy appropriately if patients are not responding to treatment. The majority of patients with myeloma have a tumour marker (either an entire monoclonal immunoglobulin or light chain) the measurement of which enables physicians to assess response to disease in a simple and timely fashion. Thus it would be clear after 3 courses of treatment if a patient had responded to Bortezomib, and that treatment could be stopped at that point if there had been no effect. This is already common practice amongst physicians using Bortezomib and could be enshrined in guidelines as will be discussed below. Clearly if treatment were limited in this way, overall cost per QALY would be reduced. Similarly it is already common practice to use Velcade in combination with intermediate doses of steroids which studies have shown to increase response rates at minimal additional cost. This again reduces overall cost per QALY in practice. Furthermore we believe it is possible to define the patient group for whom Bortezomib is most cost effective and restrict use to such patients thereby improving cost effectiveness. Such guidelines are already in operation in several regions in the UK. We believe that as a community we have mechanisms, both centrally throughout the UKMF/BCSH Guidelines committee, and locally via cancer networks to audit the application of guidelines on the cost effective use of Bortezomib, to measure outcomes and side effects. Such mechanisms are already in place in Northern Ireland and the Yorkshire Cancer Network. • We also feel that by not using Bortezomib in the relapse setting physicians will be forced to choose potentially more expensive therapies, which have not been subject to randomised, controlled trials. The options will include, for a significant number, a second high dose therapy and stem cell transplant which may associated with considerable cost, morbidity and yet is of unproven benefit. Even for the small proportion of patients who have not already received Thalidomide either as initial treatment or maintenance, the thalidomide option is	Comments noted. The Appraisal Committee considered the clinical and cost effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD. The Appraisal Committee considered the use of bortezomib in combination with dexamethasone, and this is discussed in section 4.8 of the FAD. However, guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6. Comments noted. No evidence was presented to the Appraisal Committee about the relative clinical and cost effectiveness of bortezomib compared with thalidomide. However, the Appraisal

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	costly, unlicensed, unproven, has significant side effects and thus cannot be seen as a beneficial alternative to Bortezomib.	Committee understood the difficulties highlighted in this comment, faced by health professionals caring for patients with multiple myeloma, as acknowledged in section 4.2 of the FAD.
	In summary we believe that ▪ The Apex trial does define the role of Bortezomib in the treatment of myeloma ▪ It is not necessary, nor feasible, to mount further clinical trials to establish the position of Bortezomib as a single agent in relapsed/refractory myeloma. ▪ That Bortezomib is an advance in the treatment of relapsed myeloma and can be used cost effectively for patients selected in the following way and defined in a national guideline Patient characteristics o Those at 1st relapse o With Performance status 60 o With Peripheral neuropathy < grade 2 o With Life expectancy > 12 months with treatment ▪ Stopping rules should be o After 3 cycles if non-responder o Maximum of 8 treatment cycles for responders ▪ Bortezomib should be used o In combination with dexamethasone	The Appraisal Committee considered the clinical and cost effectiveness of bortezomib treatment in accordance with the definition referred to by the consultee, and this is discussed in sections 4.4 to 4.9 of the FAD.
	This summary has universal support amongst clinicians, health care professionals, patients and their carers without dissent.	Comment noted.
Professional groups		
Royal College of Pathologists	These comments are above, in the section, 'Nominated Clinical Specialists'	
Royal College of	i) The evidence considered by the appraisal group is incomplete: Significant new abstracted evidence from	

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Radiologists	International Workshop April 2005 & ASH Annual Conference December 2005, relating to a) updated APEX trial at median 22 months follow-up confirms improved response rates (43% overall response & 16% complete response (IF-/+), as well as showing persistence of overall survival advantage for those first treated on bortezomib arm, even after cross-over [Richardson et al. Blood 2005].	The Appraisal Committee were aware of the updated results of the APEX RCT, and this publication was referenced in both the Manufacturer's Submission and Evidence Review Group Report.
	b) combination usage of bortezomib in both relapsed/refractory setting (complete responses ranging from 3-36% & overall responses 50-73%) and as up-front treatment (e.g. PAD [Cavenagh et al. 2005] gives 95% overall response & 29% complete response, as well as permitting stem cell harvest; post SCT CR increases to 57%; for non-intensive patients bortezomib/mephalan/pred [Mateos et al. 2005] gives CR 42%, without SCT, & 92% OR, which is the best complete remission rate ever described without SCT, in a representative elderly patient group). These combinations exemplify the increased efficacy that can be achieved by using novel agents together with steroids & cytotoxics, often allowing lower dosage of the costly biological modifiers to remain effective.	The Appraisal Committee considered the use of bortezomib in combination with dexamethasone and other drugs, and this is discussed in sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6.
	The evidence is also inadequate in the lack of assessment of role of poor-prognosis cytogenetics in myeloma, especially as thalidomide has been shown not to be good salvage option for myeloma patients with poor karyotype [Barlogie et al. 2003], particularly deletions of chromosome 13 & translocations of 4 & 14; however these cytogenetic translocations do not preclude bortezomib response.	The potential for a particular role for bortezomib in the treatment of patients with these genetic abnormalities was included in the evidence considered by the Appraisal Committee (see FAD section 4.11), and raised in the submissions by both nominated clinical experts. However, no cost-effectiveness evidence pertaining to this subgroup was available.
	ii) Summary of clinical efficacy does not take into account the natural history of relapsing myeloma. This is a	The Appraisal Committee was

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	progressive & often painful condition, which when advancing reduces patients functional capabilities & quality of life. Hence stabilization of disease (which approx. 60% of patients achieved on Phase II/III bortezomib trials, even with only monotherapy) can be a clinically meaningful outcome.	aware of the natural history of multiple myeloma and the importance of stabilization of disease as an outcome, having considered evidence, both written and oral, from the clinical specialists, and the Manufacturer's Submission and Evidence Review Group Report. The Appraisal Consultation Document is not intended to be a summary of all underlying evidence. Details of all evidence can be found in the Evaluation report to this appraisal.
	To preclude combined bortezomib & dexamethasone from being the main regimen under assessment seems inappropriate as this is not only the most common way that bortezomib is used in U.K., it is also recommended in the British Committee on Standards in Haematology (BCSH) guideline for bortezomib [Morgan et al. 2005].	The Appraisal Committee considered the use of bortezomib in combination with dexamethasone and other drugs, see sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6.
	Summary of cost-effectiveness appears inaccurate, not only due to aforementioned reliance on monotherapy (the ICER estimate per LYG of HDD/bortezomib combination was £28K, but this should be lower if cessation after 3 cycles in non-responders is also carried out, possibly to below £25K). There has been no apparent account of the dose-reductions often required in bortezomib treatment courses, either for neurotoxicity, thrombocytopaenia or other toxicity. The ERG data interestingly confirms the increased cost-effectiveness of bortezomib used earlier in the disease process, suggesting best efficiency if used at 1st or 2nd relapse (as per BCSH guidelines).	The manufacturer's comments on the ACD included results from a revised economic model in which costs related to adverse events were modelled (see FAD paragraphs 3.6, 4.6 and 4.7).

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	Most importantly there has been no adjustment of cost to take account of vial sharing between patients. This has been performed very successfully within my own & many other institutions, due to the excessive vial size. From the ERG analysis the estimate of patient surface area is unrealistic. The median surface area of patients is 1.7m^2 (not 2.3 m^2 as ERG appendix implies), which equates to a dose of 2.2mg per administration; this makes a saving of 38% of the vial, which can be utilized by another co-treated patient. Hence the estimated cost per course should be reduced by 38% when vials are shared in the hospital pharmacy. This would therefore equate to ICER per LYG of £15.5K, if bortezomib is used with steroid & stopped after 3 cycles in non-responders. It is also instructive to examine the data provided by ERG on varying the cost of bortezomib in the appendix. This implies that there should be strenuous efforts to both reduce the price negotiated for the drug & ideally the vial size also (if smaller practices are to avoid the need to co-schedule patients).	The cost effectiveness modelling of bortezomib compared with HDD took into account treatment restricted to patients at first relapse, stopping of treatment in non-responders, and vial sharing. This was considered by the Appraisal Committee, as discussed in sections 4.5, 4.6, 4.7 and 4.8 of the FAD.
	iii) On this basis the recommendation of the Appraisal Committee cannot be regarded as sound. Given that bortezomib has been investigated in the largest randomized controlled trial conducted in relapsed myeloma to date & this trial has been published in a preeminent peer-reviewed journal (NEJM), it is of concern that there has been no attempt by the Committee to compare this data to the alternatives that are mentioned in the documents. Thalidomide responses as a monotherapy for relapsed disease are almost universally incomplete, & range from 20-50% partial response. This option is not available for those patients who have been induced with thalidomide-containing regimens (e.g. CTD), have broken through thalidomide maintenance treatment (e.g. MRC Myeloma IX), or who have contra-indications to or intolerance of thalidomide. Repeat stem-cell transplant is only available to a small minority of patients, & retreatment with induction chemotherapy has results inferior to initial treatment [BCSH UK/Nordic Guidelines 2005]. Trials are ongoing into the use of bortezomib in induction (PAD & VISTA) as well as salvage (amendment to Myeloma IX), and enrollment into such Phase II & III trials should be facilitated, but many patients are precluded from such studies, particularly through geography &/or concomitant illness, & these individuals should not be disadvantaged in their access to licensed therapies that have proven efficacy.	Amendments have been made in the FAD, see sections 4.2, 4.7, 4.10, 4.11 and 6.1. In the STA process the evidence is provided by the manufacturer, and this did not include any alternative comparisons.
UK Myeloma Forum (Cover letter and main response)	I write on behalf of the UKMF after taking extensive soundings from the UK clinicians with a special interest in myeloma. I would make the point that myeloma is a heterogeneous disease that presents with 1º refractoriness to chemotherapy in 10% to 15% patients and this rises to 30% to 35% at relapse. Bortezomib works through novel mechanisms and is frequently effective in patients who fail to respond in chemotherapy and the available data supports the assertion that it is effective in the treatment of myeloma in early relapse. There is no enthusiasm internationally for looking at any further clinical trials with Bortezomib as a single agent and not to allow patients in the UK access to this agent on the grounds of lack of data from clinical studies, will put other novel agents such as Thalidomide and Revlimid at risk. This will again put the UK out of step with Europe and North America. I make these points on behalf of health professional in the UK responsible for managing this difficult and lethal disease. We, the members of the United Kingdom Myeloma Forum (UKMF), write as representatives of the health care	Amendments have been made to the FAD, see section 4.2. Amendments have been made in the FAD, see sections 1.1, 4.10, 4.11 and 6.1.

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	professionals who treat myeloma in the UK, and as formal consultees of the appraisal process.	
	We wish to express our disappointment with the preliminary recommendations for the use of Bortezomib in multiple myeloma in England and Wales as summarised in the recent appraisal consultation document.	Comment noted.
	Fundamental to the understanding of the approach to the treatment of myeloma is the fact that myeloma is currently an incurable disease, extremely variable in its biological pathogenesis and clinical expression. The management approach to myeloma is different to other haematological and non-haematological malignancies, where cure is the goal, and can be achieved with currently available therapy. The aim of all treatments for myeloma at the present time is to improve the quality and duration of life and that this must be taken into account when considering the role of Bortezomib.	The Appraisal Committee understood the incurable nature of multiple myeloma and its variability in biological basis and clinical expression. Amendments have been made to the FAD, see section 4.2.
	Section 1) Whether you consider that all the relevant evidence has been taken into account.	
	We acknowledge that until the publication of the APEX trial there was no robust large prospective randomised controlled trial to inform the decisions clinicians made at the point of relapse. There are however defined treatment pathways for myeloma. The choice of treatment for each patient at any one time may differ because of the heterogeneous nature of the disease, and its clinical course, and most patients will receive several treatment regimens during the course of their disease. Choice of therapy at relapse is influenced by initial treatment and the patients' response to it, the inherent characteristics of the disease, patients' performance status and their preferences. With the publication of the APEX trial physicians do now have evidence on which to base the treatment decision at relapse. The position of Bortezomib in the treatment pathway for myeloma is clear. The APEX trial has established Bortezomib as the only evidence-based standard of care for relapsed myeloma. It is the largest published randomised trial ever undertaken in relapsed myeloma and constitutes level 1 evidence.	Amendments have been made to the FAD, see sections 4.2 and 4.3.
	We believe that it should, in the group of patients we will define below, be the agent of choice for the treatment of first relapse.	Comment noted.
	Failure to recommend Bortezomib will deprive patients of the only treatment proven to increase their chance of response, time to disease progression, and overall survival relative to a proven, efficacious treatment in the relapse setting.	Comment noted.
	All alternative treatments are unproven and unlicensed in this setting, and thus expose the clinician, patient, and the NHS to unknown medical risk.	Amendments have been made to the FAD, see section 4.2 and 4.7.
	We note the Appraisal committee's recommendation that the position of Bortezomib is uncertain and that it should be	Amendments have been made

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	established more clearly by the results of on- going research. We assert however that further trials are unnecessary because the APEX trial data has unequivocally demonstrated the efficacy of Bortezomib. We are sure funding bodies would not support such trials. Clinicians would have no enthusiasm for them as they see that the role of Bortezomib as mono-therapy has already been established and are now interested in the question of how Bortezomib performs in combination with other drugs. It is necessary to clarify the role of one of the currently established national clinical trials. The MRC Myeloma IX is a key clinical trial and Bortezomib was added into the study because it was deemed to be the standard of care at 1st relapse. However the study is not intended to assess either the efficacy or position of Bortezomib as these questions have already been answered in the APEX trial. Myeloma IX simply answers questions about whether patients treated previously or not with thalidomide, or specific subgroups, (based on cytogenetics), have different outcomes. In addition it is important to be aware that less than 10% of patients nationally are eligible for entry into clinical trials either because of strict entry criteria, geographical location of the trial sites, or resource and funding restrictions. It is clear that patients should not be denied evidence-based standard of care because of their lack of access to a clinical trial.	in the FAD, see sections 4.3, 4.10, 4.11 and 6.1.
	We believe that the appraisal committee was misguided in questioning the role of High Dose Dexamethasone (HDD) in the APEX trial and we endorse its choice as a suitable comparator.	The Appraisal Consultation Document states that the Committee accepted that HDD is an appropriate comparator.
	Often used in combination with other cytotoxic agents (e.g.VAD, CVAD, ZDEX etc) both for initial treatment and at relapse, studies have shown that HDD alone is almost as effective as the combinations (80-85 % of efficacy) and is certainly the most powerful component of the combinations. This knowledge has lead to its widespread use as a single agent worldwide.	Comments noted.
	It is estimated that 70% of patients with myeloma in the UK now receive a Thalidomide containing regime as initial treatment. This markedly limits the use of thalidomide as an alternative comparator to Bortezomib at relapse and endorses the choice of HDD.That Bortezomib is more effective than High Dose Dexamethasone is therefore highly significant. We believe this shows that Bortezomib represents a major advance for patients who have commonly had as initial treatment both cytotoxic chemotherapy and, increasingly, Thalidomide. It is important that these chemo- resistant patients have the opportunity of being offered an agent which acts by an entirely different mechanism, as is the case with Bortezomib.	Amendments have been made to the FAD, see sections 4.2 and 4.9.
	Finally we believe that acknowledging the use of HDD as a valid comparator in this setting is important not only for this trial but also has major implications for future trials of new agents.	Comment noted.
	Section 2) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.	
	We suggest that the Appraisal committee has not fully taken into account a number of factors which materially affect	Comments noted.

Consultee or Commentator	Comment	Institute Response
	their conclusion that Bortezomib had not been shown to be cost effective compared with current practice in England and Wales.	
	We believe that physicians can, and will, stop therapy appropriately if patients are not responding to treatment. The majority of patients with myeloma have a tumour marker (either an entire monoclonal immunoglobulin or light chain) the measurement of which enables physicians to assess response to disease in a simple and timely fashion. Thus it would be clear after 3 courses of treatment if a patient had responded to Bortezomib, and that treatment could be stopped at that point if there had been no effect. This is already common practice amongst physicians using Bortezomib and could be enshrined in guidelines as will be discussed below. Clearly if treatment were limited in this way, overall cost per QALY would be reduced.	The Appraisal Committee considered the clinical and cost effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD.
	Similarly it is already common practice to use Bortezomib in combination with intermediate doses of steroids which studies have shown to increase response rates at minimal additional cost. This again reduces overall cost per QALY in practice.	The Appraisal Committee considered the use of bortezomib in combination with dexamethasone, and this is discussed in sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6.
	We also feel that by not using Bortezomib in the relapse setting physicians will be forced to choose potentially more expensive therapies, which have not been subject to randomised, controlled trials. The options will include, for a significant number, a second high dose therapy and stem cell transplant which may be associated with considerable cost and morbidity and yet is of unproven benefit. Even for the small proportion of patients who have not already received thalidomide either as initial treatment or maintenance, a thalidomide containing regime would be costly, unlicensed, unproven, and associated with significant side effects and thus cannot be seen as a beneficial alternative to Bortezomib.	Amendments have been made to the FAD, see section 4.2, 4.7 and 4.9.
	W e believe it is possible to define the patient group for whom Bortezomib is most cost effective and that mechanisms are already in place both nationally through the UKMF/ BSCH guidelines group to disseminate such advise. We believe that there are also systems in place locally through Cancer Networks to ensure implementation of such advice. We are indeed aware that regional groups already have such mechanisms in place where usage, outcomes, and side effects are being audited.	Comments noted.

Consultee or Commentator	Comment	Institute Response
	We submit that all of these factors should be taken into account 'on the other side of the equation' when assessing the overall cost per QALY.	Comment noted.
	Section 3 Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS We do not agree with the provisional recommendations of the appraisal committee but take the view that	
	▪ The APEX trial does define the role of Bortezomib in the treatment of myeloma	This is discussed in FAD sections 4.2 and 4.3.
	▪ It is not necessary, nor feasible, to mount further clinical trials to establish the position of Bortezomib as a single agent in relapsed/refractory myeloma.	This is discussed in FAD sections 4.10 and 4.11.
	▪ That Bortezomib is an advance in the treatment of relapsed myeloma and can be used cost effectively for patients selected as defined below	This is discussed in FAD sections 4.3 and 4.4 to 4.12
	▪ That the mechanisms for enforcing its use in this defined way are in place.	This is discussed in see FAD sections 4.4 and 4.6.
	Definition of role and position of Bortezomib o Patient characteristics - Those at 1st relapse - With Performance status >60 - With Peripheral neuropathy < grade 2 - With Life expectancy > 12 months with treatment - o 'Stopping rules' should be - After 3 cycles if a non-responder - Maximum of 8 treatment cycles for responders - o Bortezomib should be used - In combination with dexamethasone	The Appraisal Committee considered the clinical and cost effectiveness of bortezomib treatment in accordance with the definition referred to by the Consultee, and this is discussed in sections 4.4 to 4.9 of the FAD.
	In the light of the above we urge the appraisal committee to revise its' preliminary recommendations and to recommend the use of Bortezomib for use in relapsed and refractory myeloma in the way defined in this document.	Comment noted.

Consultee or Commentator	Comment	Institute Response
Patient/Carer groups		
International Myeloma Foundation (UK) (Cover letter for joint response)	IMF (UK) represents 15,000 patients and carers across the UK and provides a wide range of services including, but not limited to: • an information line, that takes 500 calls a month • a network of 35 patient and family support groups, • patient and family infodays, of which seven are held annually across the country • a website, which has taken 800,000 visits from UK residents in 2006 already, We do all we can to help myeloma patients and their families deal with everything a diagnosis of myeloma throws at them. Myeloma is a potentially devastating, complex an difficult cancer both to live with and to treat, which attacks and destroys bone, ravages the immune system and causes organ failure. The potential of a drug such as bortezomib, that is not only clearly active, but increases life expectancy, and crucially improves the quality of life of patients and their carers, cannot be over emphasised. Our submission is made jointly, with other patients organisations and ewe stand shoulder to shoulder with the entire myeloma and cancer community in terms of the unacceptability of this preliminary decision. We urge NICE to make the right decision.	Comments noted.
Leukaemia CARE (cover letter for joint response)	Overall we believe that the report by the Evidence Review Group – (ERG) - (Southampton Health Technology Assessment Centre – SHTAC) provides both a thorough and fair review of the available clinical evidence base. However as a patient organisation we are obviously disappointed to see that the NICE appraisal committee failed to give positive guidance on the use of bortezomib for multiple myeloma. We fail to understand how the appraisal committee has reached a different conclusion to the British Committee on Standards in Haematology (BCSH) as demonstrated in their recent position statement having reviewed the same clinical evidence. The lack of a truly effective treatment for patients at first relapse, and the failure of NICE to give positive guidance to bortezomib, could subject many myeloma patients to a premature death, or at the very least it will force patients into private healthcare where bortezomib is widely available leading to a two-tier health care system. Many patients may be forced to sell personal possessions in order to fund their treatment. This is clearly an unacceptable situation in the light of the ambitious and forward thinking ideals laid out in the Cancer Plan 2000, presented by Alan Milburn.	Comments noted. Comments noted. Comments noted.

Consultee or Commentator	Comment	Institute Response
	One of his key tenets was to ensure that England would no longer lag behind Europe in its approach to the treatment and care of patients with cancer, and to ensure equity of treatment notwithstanding the background or class of the person suffering from the disease – clearly this is not the way to do that! In order to minimise the volume of appeals that the NICE Committee will have to review, I have submitted my appeal to this decision as a joint document with the International Myeloma Foundation, The Leukaemia Research Fund and cancerbackup. I hope that the comments we make in our appeal document are helpful for the Appraisal Committee and would like to restate the fact that in its review of the evidence the ERG were very positive about the use of bortezomib in multiple myeloma.	These responses to the Appraisal Consultation Document were considered by the Appraisal Committee at the second meeting for this appraisal on 6 September 2006. Appeals can be made during the Appeal Period after the Final Appraisal Determination is issued.
Leukaemia Research (cover letter for joint response)	Leukaemia Research has joined IMF (UK) and Leukaemia Care in submitting a joint response to the STA ACD on bortezomib for multiple myeloma. We would wish to make the following additional points. The Leukaemia Research myeloma cytogenetics database located at Salisbury and headed by Dr Fiona Ross is a unique resource. The database is closely integrated with the current myeloma trials in a way which offers unprecedented opportunities to correlate biological features of the disease with responses to therapy. If the effect of the ACD (translated unaltered to an FAD) were to be reduction of entry into trials, or even patchy entry, this would greatly compromise this prospect. The joint submission has proposed that bortezomib should be approved for use at first relapse with detailed follow-up studies – the existence of the myeloma cytogenetics database will greatly enhance the effectiveness of such a follow-up program. Leukaemia Research would refer the appraisal committee to the precedent set in the transition from ACD to FAD for imatinib for treatment of chronic myeloid leukaemia. It is appreciated that, in the case of drugs with novel modes of action, it is particularly difficult to achieve effective comparison with existing treatments. We are concerned that this does not act to the disadvantage of patients and would urge the committee to, once again, take the path which will encourage development of novel therapies. This is particularly vital in instances such as myeloma, where there is a general agreement that existing therapies are far from optimal.	Amendments have been made in the FAD, see sections 1.1, 4.10, 4.11 and 6.1. Amendments have been made to the FAD, see section 4.2.

Consultee or Commentator	Comment	Institute Response
Joint Patient Interest Group Submission: International Myeloma Foundation (UK) Leukaemia Research Leukaemia CARE Cancer Backup	**Overview**	
	IMF (UK), Leukaemia CARE, Leukaemia Research Fund and Cancerbackup believe that the length, and quality, of life for patients with myeloma will be reduced if NICE confirms the preliminary guidance in the ACD. We believe that no patient with myeloma should die without having access to bortezomib if it is what the treating physician, in consultation with the patient, believes is the appropriate therapy.	Comment noted.
	We welcome the opportunity to respond to the ACD and to provide further information and clarification to assist NICE in making an informed and positive final decision.	
	Jointly with the other stakeholders in the myeloma community we urge NICE to reconsider its position in light of the important points outlined in this response.	Comment noted.
	In summary, the decision does not appear to have fully considered the realities of clinical practice in myeloma, or the potential impact of its decision on patients for whom bortezomib is an important therapeutic option.	Comment noted.
	Summary of our response:	
	• Bortezomib should be approved as a treatment at first relapse, within its licensed indication, as per the Evidence Review Group's (ERG) findings and as per the BSCH position statement.	Comment noted.
	• In addition to the survival benefit, bortezomib is demonstrated to have no greater detrimental impact on quality of life than high-dose dexamethasone. Bortezomib showed a trend towards decreased number of grade 3 and greater infections, and prevented further bone destruction.	Comment noted.
	• Bortezomib can prolong the time to disease progression in patients with relapsed myeloma.	Comment noted.
	• Level one evidence from the APEX trial demonstrated that bortezomib is most clinically effective at first relapse, with respect to chance of response, time to disease progression and one-year survival.	The Appraisal Committee understood that bortezomib monotherapy is clinically effective compared with HDD at both first and subsequent relapse, and more cost effective at first relapse compared with

[1] CancerStats Monograph 2004, Cancer Research UK

[2] Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005; 352(24): 2487-98

Consultee or Commentator	Comment	Institute Response
		subsequent relapse, see sections 4.3 and 4.5 of the FAD.
	• Bortezomib is most cost effective when used at first relapse, and introducing a stopping rule will avoid patients whose disease is not sensitive to proteasome inhibition being given unnecessary treatment and will reduce the cost per patient of treatment.	The Appraisal Committee considered the clinical and cost effectiveness of restricting treatment to patients at first relapse, and stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD.
	• Bortezomib offers a completely novel mode of action. It is therefore extremely important in treating patients, many of which are chemo resistant by the time they reach first relapse.	Amendments have been made in the FAD, see section 4.2.
	• The proposals in the draft guidance for further trials are neither practicable, nor ethical. The evidence in favour of bortezomib in relapsed patients is too strong to permit clinicians to randomise patients to receive alternative unproven treatments. Since the only drug licensed for this indication is high-dose dexamethasone, which has been demonstrated inferior to bortezomib, trials testing this comparison are unethical. In addition, only around 10% of patients access trials.	Amendments have been made in the FAD, see sections 1.1, 4.10, 4.11 and 6.1.
	• The failure to recommend the use of bortezomib is perverse and will leave patients without an effacious and licensed treatment option.	Comment noted.
	• Every patient, regardless of where they live or their individual circumstances should be entitled to receive those treatments recommended to them by their consultant, provided there is strong clinical evidence of their effectiveness. If, as NICE proposes, the only use of bortezomib should currently be in clinical trials, patients not eligible for trial participation but eligible under the licensed indication to receive the product would not be able to access it.	The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness. Any new treatments recommended should be cost effective compared with existing treatments.

Consultee or Commentator	Comment	Institute Response
	• Phase IV trials evaluating the true role of bortezomib in routine clinical practice should be implemented with appropriate funding provided by the Department of Health.	Comment noted.
	Living with multiple myeloma	
	An estimated 3,727[1] new cases of myeloma are diagnosed each year in England and Wales. The causes of myeloma remain unknown. Like most types of cancer, myeloma is more common in older people and it is unusual for myeloma to be diagnosed in people under the age of 50. Myeloma is a disorder of the plasma cells. Blood cells are constantly generated. With myeloma, the production of new cells becomes out of control and large numbers of abnormal plasma cells are produced. These fill up the bone marrow and interfere with production of normal white cells, red cells and platelets. Several, or many, areas of bone may be affected. Myeloma causes thinning of the outer bone, fractures and pepper pot lesions in bone which are extremely painful. The main symptom of myeloma is often back pain as it commonly affects the bones of the spine. Patients may also eperience loss of height. Other bones may also be affected such as the ribs, neck or pelvis. Other symptoms may include any of the following: • excessive tiredness and lethargy due to a lack of red blood cells in the blood (*anaemia*) • kidney problems caused by the paraproteins produced by the myeloma cells. Kidney damage can increase tiredness and anaemia • repeated colds, coughs and other infections (particularly chest infections) because of a shortage of normal antibodies • weakening of the bones by the myeloma cells, which may increase the risk of fractures • loss of appetite, feeling sick, constipation, depression and drowsiness caused by too much calcium in the blood (*hypercalcaemia*). The excess calcium is released into the blood from the damaged bones • unexplained bruising and abnormal bleeding (nosebleeds or bleeding gums) because the number of platelets in the blood has decreased • pins and needles, numbness, tingling or weakness in the feet or legs, difficulty passing urine or opening the bowels. Any of these symptoms could mean that a myeloma tumour is pressing on the spinal cord (known as *cord compression*).	Comments noted.
	Current treatment options for myeloma Myeloma is rarely curable, but it is treatable, and treatment can be very effective at controlling symptoms and stopping the development of the disease. Chemotherapy, usually combined with steroids, is the main treatment for myeloma. Many patients may benefit from high-dose chemotherapy. For this treatment, some of the blood stem-cells are removed, often from the blood but	

Consultee or Commentator	Comment	Institute Response
	sometimes from the bone marrow, before the high-dose chemotherapy. They are given back through a drip after the high dose chemotherapy treatment. This is known as a stem-cell or bone marrow transplant and can help some people to stay in remission, but it is an intensive treatment that is not suitable for everyone. After chemotherapy, interferon or steroids may be used to help keep the myeloma in remission. Thalidomide although unlicensed, has in the last decade been found to be effective in controlling myeloma that has come back after chemotherapy. Thalidomide is also being tested as an initial treatment. Drugs known as bisphosphonates are commonly used to reduce bone damage caused by the myeloma and to help bones to heal. They are also very helpful in lowering raised calcium levels in the blood. They can be given alongside chemotherapy or after chemotherapy has finished. They may also be given to help prevent bone damage from occurring. Radiotherapy may be used to strengthen the bone and reduce pain in the affected areas. Surgery may also occasionally be used to strengthen weakened bones, to prevent fractures or, rarely, remove areas of myeloma that are pressing on important areas of the body such as the spinal cord. **Bortezomib** Bortezomib is a new type of anti-cancer drug called a proteosome inhibitor. It is given to people who have already been treated with at least one other type of chemotherapy and who have already had, or are unsuitable for a bone marrow transplant, but whose myeloma has continued to develop. Proteosomes are a group of enzymes found in all cells in the body. They have an important role in controlling cell function and growth. By interfering with the function of proteosomes, bortezomib may cause cancer cells to die and may stop the cancer from growing. Bortezomib is usually given intravenously, as four doses over a three-week period. The APEX study was designed to confirm the efficacy and safety of bortezomib in patients who had previously received between one and three therapy treatments (not bortezomib). Patients were randomly assigned to receive bortezomib or a standard high-dose treatment of dexamethasone. Early results of the APEX study of 669 patients with relapsed or refractory myeloma dramatically favoured bortezomib and, in fact, the trial was halted early because of the distinct divergence between the bortezomib and dexamethasone arms. This study reported superior median time to progression, where time to progression was nearly twice as long in those taking bortezomib as against those taking dexamethasone (6.2 months versus 3.5 months for the dexamethasone group)[2]. More importantly in an update to the original report, the overall survival reported on the bortezomib arm was 29.8 months compared to 23.8 months despite 66% of the HDD patients being crossed over bortezomib, but being measured on the dexamethasone arm. This trial clearly showed that patients had an increased chance of response	Comments noted.

Consultee or Commentator	Comment	Institute Response
	and prolonged survival at first relapse compared to later on in their disease. In the update to the APEX study 43% of patients on this trial had a complete or partial response to bortezomib. The original trial reported a response rate of 18% to dexamethasone, which was not followed up in the update as most patients had crossed over to bortezomib at that point.	
	1. Whether you consider that all of the relevant evidence has been taken into account	
	We consider that some evidence has been either misinterpreted or misunderstood. Please consider the following additional points: **1.1 Patient Impact**	
	The preliminary recommendation outlined in the ACD would have a serious detrimental impact on patients and their carers.	Comment noted.
	• Bortezomib has been demonstrated in randomised trials to offer an appreciable extension of time to progression and survival to patients with relapsed myeloma.	Comment noted.
	• The area of relapsed myeloma represents an area of unmet clinical need and failure to approve bortezomib will deprive myeloma patients of an effective therapy.	Comment noted.
	• In the absence of a formal QOFL assessment we believe note should be taken of the reduced number of serious adverse reactions, and a lesser degree of bone destruction with bortezomib should be highlighted.	Comment noted.
	• To restrict use of bortezomib to clinical trials will effectively render its availability to all NHS patients dependent on local policies of Primary Care Trusts; this is precisely the problem of "postcode prescribing" which was cited as one of the key reasons for establishing NICE.	Comment noted.
	• A decision not to recommend bortezomib would effectively mean that few patients will have access to this effective treatment, as fewer than 10% of patients ever get access to clinical trials.	This is discussed in FAD section 4.10.
	1.2 Clinical Trials	
	The ACD indicates a recommendation for further trials and for bortezomib to be restricted to trial usage only. While we support the principle of testing new treatments in clinical trials, bortezomib has been shown to offer significant benefits over any other viable comparator. Further trials in this context are neither practicable, nor indeed ethical for the following reasons:	This is discussed in FAD sections 4.3, 4.10 and 4.11.
	• APEX is the largest and most robust trial ever conducted in myeloma and constitutes level one evidence, which guides clinical practice with respect to sequencing of treatments.	

Consultee or Commentator	Comment	Institute Response
	• Following a pre-planned interim analysis of time to progression (TTP), the HDD arm of the APEX trial was halted early and all patients were offered bortezomib regardless of disease status. Because of the obvious improvement in response rates in the bortezomib wing of the study, it was considered unethical not to offer bortezomib to all participants. • Both the ERG and the ACD acknowledge that bortezomib is clinically superior to high- dose dexamethasone (HDD) – which would make any further trial comparing bortezomib with HDD unethical. • The evidence from APEX is already sufficiently strong to eliminate "therapeutic ambivalence" which is an ethical imperative to enter patients into randomised controlled trials. • The recommendation that trials should be undertaken comparing bortezomib with current standard practice would not be feasible for the following reasons: - HDD is criticised in the ACD as a choice of comparator - We are not aware of any licensed treatment which would be eligible for use in a comparison arm of such a trial (thalidomide is not licensed for this indication) - Patients not eligible for trial participation, but eligible under the licensed indication to receive the product, would not be able to access it. • We would anticipate that the standard of care by the time any possible trials would be reported will be to use both thalidomide and dexamethasone and cyclophosphamide as induction, negating their use in first relapse and rendering trials comparing bortezomib with these treatments of no clinical relevance. • For the majority of patients, the revised MRC Myeloma IX protocol represents the only trial option in the next 2-3 years that incorporates bortezomib. Many Trusts/Networks have blocked access to this trial because of the perceived costs of the treatment options and because of the operational costs associated with analysing and reporting data. Current evidence strongly suggests that less than 10% of the myeloma community will be entered into this trial. • The MRC IX trial was not designed to answer scientific questions on where best to use bortezomib – the bortezomib sub-protocol amendments will only answer questions on the impact of treating patients previously treated with thalidomide or not. The relapsed protocol is not randomised, or compulsory, and is therefore not relevant. • Initiating a major, new clinical trial is an enormously time-consuming and bureaucratic process - from outline to first entry of patients would be 18-24 months at best – and may be impossible if funding and a sponsor cannot be obtained. During the trial development process under the proposals set out in the ACD, the majority of patients would go without a licensed treatment option. Furthermore, for the reasons stated above, it is likely that such a trial would be refused ethical approval and, if approved, it is likely that many clinicians would refuse on ethical grounds	Comment noted. Amendments have been made in the FAD, see sections 4.10 and 4.11. Comments noted. Amendments have been made in the FAD, see sections 4.10 and 4.11. Comments noted. Amendments have been made in the FAD, see sections 4.10 and 4.11.

Consultee or Commentator	Comment	Institute Response
	to enrol patients. • A further difficulty with designing and interpreting any such trials is the high probability that, by the time any trial is completed, immunomodulatory drugs (IMiD's) will be entering wider clinical use and the comparisons would be out of date. The trials would then be subject to the same criticisms as are made in the current ACD concerning the use of HDD as a comparator arm. Bortezomib should be available as a treatment option in order to progress clinical trials over the next five years and arguably it should become the standard comparator for future trials. To restrict the use of bortezomib to clinical trials will therefore effectively render its availability to all NHS patients dependent on local policies of Primary Care Trusts; this is precisely the problem of "postcode prescribing" which was cited as one of the key reasons for establishing NICE.	Amendments have been made in the FAD, see sections 4.10 and 4.11. Comment noted.
	2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate…	
	2.1 Cost Effectiveness factors There are a number of points we urge NICE to consider: • The health outcomes data in the manufacturer's submission and the ACD did not take into account a stopping rule at three cycles in non-responding patients. Introducing such a stopping rule would significantly reduce the cost/QALY. • The health outcomes data in the manufacturer's submission and the ACD did not take into account the addition of dexamethasone. This would reduce the cost per QALY. The ERG recognised that the addition of HDD improved cost effectiveness and although bortezomib is only licensed as mono-therapy, it is, in practice, most widely used in combination (and HDD is referred to in the SPC).	The Appraisal Committee considered the clinical and cost effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD. The Appraisal Committee considered the use of bortezomib in combination with dexamethasone, and this is discussed in sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6

Consultee or Commentator	Comment	Institute Response
	• The extremely low cost of HDD compared to other possible treatments artificially inflates both the ICER and the comparative cost per QALY. NICE must be able to consider comparisons of expensive new treatments with older, cheaper, treatments in a more meaningful way.	Comment noted.
	• When compared with the cost of an autologous transplant - which is noted in the ACD as a potential treatment for myeloma at first relapse, the cost of a single course of bortezomib is significantly lower.	Comment noted.
	• As new treatments are incorporated into practice and clinicians become better able to manage their side effect profiles, associated quality of life for patients improves. This will have a favourable impact on cost per QALY and NICE should consider the lifetime of a drug rather than the first use in clinical trials.	Comment noted.
	• The rigid applicability of a maximum QALY of £30,000 to this appraisal is questionable. We would expect NICE to accommodate a new drug in an uncommon cancer in a similar way to which it would deal with a treatment for an orphan disorder.	Comment noted.
	2.2 Comparator of HD Dexamethasone (HDD)	
	The ACD criticises the choice of HDD as a comparator – at the time the trial was initiated this was the only licensed drug for myeloma and therefore the only one appropriate for a registration trial. HDD is used by a number of international study groups including SWOG and ECOG as a comparator in the field of myeloma. Other new therapeutic agents indicated for myeloma will also use HDD as a comparator.	The Appraisal Consultation Document states that the Committee accepted that HDD is an appropriate comparator.
	2.3 Clinical Audit	
	We have already made the case that the trials that are recommended in the draft guidance are neither practicable, nor ethical. We believe that there is a strong case to recommend making the drug available with an accompanying requirement that there should be ongoing data collection and review of cost-effectiveness.	Comment noted.
	3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS…	
	3.1 Objections to initial recommendation	
	In myeloma, there are a variety of bespoke pathways to accommodate the heterogenous nature of the disease in patients with this complex, debilitating cancer. We believe that the appraisal committee has not fully understood the reason for the more complex treatment pathways for this group of patients.	Comment noted.
	For all the reasons outlined above, the ACD does not reflect the best interests of patients and their carers and does not	Comment noted.

Consultee or Commentator	Comment	Institute Response
	take appropriate account of all the available evidence.	
	4. Declarations of Interest	
	• Cancerbackup has received sponsorship for several publications and projects from Ortho Biotech, the manufacturer of bortezomib. • IMF (UK) receives an unrestricted educational grant from Ortho Biotech to use across its range of services • Leukaemia CARE has received an unrestricted educational grant from Ortho Biotech towards the running costs of our Patient Conferences, and we also receive a regular supply of unbranded patient information leaflets on Cancer related Fatigue, Work and Cancer, and Understanding Myeloma.	Comments noted.
Other consultees		
Department of Health	Please see below a summary of the detailed comments I have received from the Department of Health's clinical advisors on cancer topics. I have also attached detailed comments for your reference and information. **Issues with Treatment Pathway** There is a need to present a clear treatment pathway for the patient group and where bortezomib is in the treatment schema. You maybe aware that the British Committee for Standards in Haematology (BCSH) has shown a relatively clear way forward, and it is suggested that the appraisal committee consider adopting/supporting their approach **Impact on clinical trials** Concern was expressed that NICE's recommendation on further research may be seen as a 'negative' endorsement and will encourage trusts/networks to refuse to sanction participation/entry into UK trials which will undermine availability of further trial data. **Full detailed comments from Department of Health's Clinical Advisors for National Institute for Health and Clinical Excellence's Technology Appraisal Document on Bortezomib for Multiple Myeloma.** **Comments from first Clinical Advisor**	The BCSH/UKMF/Nordic guidelines (2005) and of the BSCH position statement (2005) on bortezomib in multiple myeloma were brought to the Committee's attention through the Manufacturer's Submission and Evidence Review Group Report. Amendments have been made to the FAD, see sections 1.1, 4.10, 4.11 and 6.1.

Consultee or Commentator	Comment	Institute Response
	It is difficult to find flaws with the arguments and this reflects the way that the data is presented. The conclusions however are perverse and would not be popular with the haem-onc community.	Comments noted.
	The main problem I suspect was the inability of the clinical representatives to present a clear treatment pathway for treatment of this group. The committee quite rightly pointed out that treatment depends on initial response, age and co-morbidities and on this basis a logical treatment pathway can be constructed. The BCSH have shown a relatively clear way forward and it is a shame that such an approach was not adopted and supported as a way ahead to the committee.	Comments noted.
	The committees understanding of the APEX study was also disappointing. They point out early on the quite remarkable results with a doubling of response to disease progression time (6.2 v 3.5 months) but fail to develop the significance of this. This was a Phase III study of over 600 relapsed patients. Although a mixture of early and late relapse the results do support a better response in the early phase of the disease, as opposed to later relapse, and the data would support a better cost per QALY in this group. The company perhaps made an error in presenting life years gained (LYG) as opposed to QALYs, as this ignores the potential problems with neuropathy in responders, but I suspect that this would have only made a small difference.	The Appraisal Committee considered the evidence for the clinical effectiveness of bortezomib monotherapy, and this is discussed in section 4.3 of the FAD.
	The differences in QALY would particularly be highlighted if, as suggested, treatment is stopped after 3 courses if there is no evidence of response. The London Cancer New Drugs Group certainly came to this conclusion on the evidence. There does therefore appear to be a clear case for supporting its use in first (or early relapse).	The Appraisal Committee considered the clinical and cost effectiveness of restricting treatment to patients at first relapse only, and stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in sections 4.5 and 4.6 of the FAD.
	We are entering an era of a number of important agents in myeloma that will potentially transform the result in this group. If Bortezomib is not supported then it is unlikely that we will be able to introduce any of the newer agents in the foreseeable future…….. What this essentially means is that not only will we not be able to offer this agent but thalidomide (should it obtain a licence) and revlimid (when it does) will equally be unavailable. This will be unacceptable when we look at practice in North America and Europe. While this may save money it is not in patients'	Comments noted.

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	interests and the arguments to support the decision are not sustainable when the data on which the decision is made is more clearly analysed. I make these points as a haematologist who is no longer involved in treating this patient group and has no conflicts of interest. **Comments from second Clinical Advisor** Failure to recommend the use of Bortezomib within its licensed indication except in well designed clinical studies is not a conclusion that is likely to be accepted or acceptable - and is disappointing in the circumstances. I understand the strict academic correctness of the conclusion but the committee appear not to have not truly understood the realities of where we are in clinical practice and the demands/expectations of a highly informed and motivated patient and patient advocacy community. Further trial data are, of course, essential - a standard for treatment stated in the UK/Nordic Myeloma Guidelines is that patients should be treated in clinical trials/studies wherever possible; the reality is that it is only a minority of English/UK patients who have the opportunity to be entered in trials. Currently there are trusts and networks who have not sanctioned entry of patients in to Myeloma 9 because of perceived excess treatment costs with Thalidomide. The revised NCRN Myeloma 9 protocol represents the only viable Bortezomib trial option in the next 2-3 years for the majority of NHS patients in England (& the UK) - however, it is inevitable that some trust/networks will currently refuse to allow the amendment to assess Bortezomib because of excess treatment costs. In context, therefore, this report from NICE, as drafted, will be seen as a "negative" endorsement and will simply encourage trusts/networks to refuse to sanction participation/entry into this important and hitherto successful UK trial - it will simply undermine any likelihood of further helpful trial data being available by 2009 and further exacerbate the postcode lottery situation. New trials for review in 2009 are not a viable UK option. Initiating a major, new clinical trial in an enormously time-consuming and bureaucratic process - from outline to first entry of patients would be 18-24 months at best - assuming the investigators can get funding and a sponsor - any such funding should not exclusively be from Ortho-Biotech and the sponsor would have to be a major academic institution. Thus pressure on UK clinicians even in academic institutions is such that UK based Bortezomib trials other than amended Myeloma 9 are not going to emerge in the near future because of the above. Thus any data will have to emerge from other international studies and the UK will be seen as being set back from being involved in leading and innovative clinical research. It would be preferable to be more specific in the recommendation – that Bortezomib is not recommended for fist line myeloma treatment or primary refractory patients except in well - designed clinical studies.	Comment noted. Comment noted. Comment noted. Amendments have been made in the FAD, see sections 1.1, 4.10, 4.11 and 6.1. Guidance is given by NICE within the boundaries of the licensed indication. See Guide to the Methods of Technology Appraisal

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		http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6.
	With functioning Cancer Networks in England it should be possible to audit the use and outcomes of Bortezomib usage within its licensed indications, given in accordance with BCSH/Nordic Myeloma guidelines subject to documented approval through MDT's - invoking a mandatory audit process would be both a sanction on inappropriate usage and a means to collect actual clinical data which would perhaps be more representative of practice than data form clinical trials.	Comments noted.
	Having had reasonable clinical experience with Bortezomib I am more aware of situations wherein I would not consider its usage and - and I would declare an interest as a practising clinician in myeloma from the experience of seeing a current group of late relapse patients responding well - in one case achieving remission when other therapies were clearly failing.	Comment noted.
DHSSPS NI	I disagree with the ACD recommendations for bortezomib in its licensed indication. The clinical effectiveness of bortezomib cannot be in doubt that this is acknowledged in the ACD. Furthermore the committee have not rejected its use on cost effectiveness grounds. The recommendation appears therefore to be based upon the lack of clarity regarding the position of bortezomib in the pathway of care for patients with myeloma.	Amendments have been made in the FAD, see sections 4.2 to 4.7.
	I believe this is perverse as the management of patients, where there is a potential choice of therapies, will depend on the relative toxicities of those treatments, clinical effectiveness, and patient factors such as pre-existing comorbidity. It would not have been unreasonable for the committee to suggest that bortezomib should be restricted for use in patients where the use of high dose dexamethasone would be considered an appropriate treatment option, given that this was the standard treatment arm of the APEX trial which confirmed the clinical effectiveness of bortezomib.	Comments noted.
	In randomised phase II trials where Time to Progression is the primary endpoint of the trial it is increasingly common for patients receiving standard care to cross over to the experimental treatment where this has shown an advantage. This crossover occurs because of ethical considerations. Therefore if the committee accept that time to progression is a valid primary endpoint in a clinical trial they should accept the data as presented. Crossover will always make analysis of some secondary endpoints such as overall survival difficult to analyse satisfactorily.	In the Appraisal Consultation Document, the Committee concluded that bortezomib has shown clinical benefits compared with HDD. This evidence for clinical effectiveness for bortezomib monotherapy is discussed in section 4.3 of the FAD.
	The committee suggest that they believe the manufacturers estimate for cost effectiveness of £38,000 per QALY is an underestimate and that they were not persuaded that bortezomib was cost effective compared to current standard treatments used in the NHS. If this is the prime reason for not recommending bortezomib this should be stated in section 1.	Amendments have been made in the FAD, see sections 4.7 and 4.12.

Consultee or Commentator	Comment	Institute Response
	Finally, given the ongoing trials of bortezomib in multiple myeloma, and the data which will be available from these in the near future, the suggested review date of 2009 is too late to adequately react to a rapidly changing clinical environment. Without early review of the final appraisal (assuming the recommendations in the ACD remain unchanged) patients with myeloma may be significantly disadvantaged compared to other parts of Europe or even the British Isles.	This date has been changed in the FAD, see section 8.2.
Welsh Assembly Government	1. There are several important issues that need to be considered:- • Bortezumib is undoubtedly an effective treatment for Myeloma; • Bortezumib may work when other treatments have failed but in the UK practice is seldom used in first relapse; its precise timing is uncertain; • There is growing evidence that Bortezumib is more effective in combination rather than as a monotherapy; • The problems in relapsed and primary refractory Myeloma are not necessarily the same. 2. In the light of this, support is given to the decision not to endorse Bortezumib Monotherap as the treatment of Myeloma in first relapse. The results of the study to Myeloma IX will shed alot of light on this question and should be fully supported - but it uses Bortezumib in combination with High Dose Dexamethasone (HDD). 3. There will be a cohort of patients already in the UK who have had multiple relapses - possibly after high-dose Melphelan - or who have been shown to be refractory to several other regimes. These patients are excluded from the Myeloma IX study by their current disease status but should not be denied the chance of a worthwhile response from Bortezumib. The recommendations need to have an additional paragraph that addresses the needs of these patients and allows them the use of Bortezumib +/- HDD. 4. The draft rightly criticises the relative usefulness of Bortezomib vs Dexamethasone at first and subsequent relapse on the grounds that there are other effective and cheaper options. 5. What is still clear to clinical haematologists is that for a significant number of patients who have already received all the options (more first line treatment CTD / MP, VAD, 2nd high dose etc) Bortezomib produces a useful response. If this draft is agreed then Bortezomib will be unavailable for a large group of patients for whom it is the only prospect of another year or 2 of life. There are no trials in Wales in relapsed myeloma and trials of 'last line' therapy vs placebo cannot happen once there is phase 2 data: It would be useful to try and agree the following:- • a set of criteria on when to give up Bortezomib in patients who are not showing sufficient response; and • a decision not to use it again when patients progress.	Comments noted. Comments noted. The Appraisal Committee considered use of bortezomib at late stages of relapse when disease may be refractory to many alternative therapies (see FAD section 4.2 and 4.3) Comment noted. The Appraisal Committee understood that bortezomib can be effective in patients who have relapsed after several treatments, and that this may be related to its novel mode of action. It considered the cost-effectiveness of use at late relapse, as discussed in section 4.5 of the FAD. The Appraisal Committee considered the clinical and cost

Consultee or Commentator	Comment	Institute Response
		effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, as discussed in section 4.6 of the FAD.

Reply received but no comments:

- Royal College of Nursing of the United Kingdom