NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Bortezomib monotherapy for relapsed multiple myeloma – POST APPEAL

Response to comments received from consultees, commentators and the public on the post appeal Appraisal Consultation Document (May 2007 ACD)

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Janssen-Cilag (CIC removed version)	Janssen-Cilag welcomes the Appraisal Committee's further consideration of bortezomib for the treatment of relapsed multiple myeloma, including its review of our proposal to implement a response scheme that would allow bortezomib to be made available to eligible patients in circumstances where the cost of such treatment would be borne by the NHS only for patients who developed a response to therapy. However, we have some important concerns with respect to the Committee's assessment of the evidence for bortezomib and the draft recommendations proposed in the ACD. We believe that patients with relapsed multiple myeloma, who have extremely limited treatment options should be permitted access to this clinically effective, innovative treatment, which offers a proven survival advantage in this devastating cancer. We believe that bortezomib is cost effective when assessed by reference to its standard UK list price, as demonstrated by the fact that the ICERs produced are within the range considered by NICE to represent an appropriate use of NHS resource in comparable appraisals. However, despite this belief and in order to ensure that bortezomib may be made available to all patients who may benefit from therapy, Janssen-Cilag has proposed a novel response scheme, which further improves the cost effectiveness of the product. In accordance with Janssen-Cilag's response scheme, which is supported by the Department of Health and Welsh Assembly Government, the company would rebate the costs of bortezomib in those patients who do not respond after up to 4 cycles of treatment. However, while the Appraisal Committee has considered the scheme proposed by Janssen-Cilag, it has rejected this in favour of a second scheme devised, we believe improperly, by the Institute.	Comment noted.

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	We set out below our comments on the approach followed by the Appraisal Committee in relation to the response scheme before considering further issues raised by the content of the ACD. **1. <u>The approach of the Appraisal Committee to Janssen-Cilag's response scheme</u>** The company has significant concerns about the fact that the Appraisal Committee has sought to produce its own response scheme, which would appear to be outside the powers available to the Institute. The approach proposed by NICE would deny access to a group of patients who have achieved a significant clinical outcome and is, in our view, inappropriate in circumstances where the inclusion of such patients delivers a cost per QALY well within the range that has been considered to be acceptable by NICE in other comparable cases.	This comment has been superseded by the agreement of a final response scheme between the manufacturer and the Department of Health.
	1.1 <u>NICE has sought to modify the Janssen-Cilag Response Scheme</u> The response scheme proposed by Janssen-Cilag (and endorsed by the Department of Health and Welsh Assembly Government in letters to NICE dated April 25th and May 4th 2007, respectively) provided that the company would rebate the cost of bortezomib therapy in those patients who had not developed a complete response (CR), partial response (PR) or minor/ minimal response (MR), as determined by levels of serum M-protein, within four cycles of treatment. This scheme is fully transparent; its objective is to ensure that bortezomib is made available to all patients who will derive benefit in a manner that is cost-effective for the NHS and acceptable to the company. Treatment through the Janssen-Cilag scheme results in a cost per QALY for bortezomib of £27,000, well within the range of values that have been considered acceptable for other treatments recommended by NICE. However, the Appraisal Committee has rejected this proposed scheme (paragraph 4.12 of the ACD) and instead suggested that bortezomib should be recommended for use in NHS patients only in accordance with a second scheme, which was not that proposed by Janssen-Cilag (paragraph 1.1 of the ACD). We do not believe that the Appraisal Committee is permitted to make such a recommendation in accordance with the powers delegated to the Institute. The Secretary of State and the Welsh Assembly Government have directed NICE "*to appraise the clinical benefits and the costs of such healthcare interventions as may be notified by the Secretary of State or the [Welsh Assembly Government] and to make recommendations…*" (Directions to the National Institute for [Health and] Clinical Excellence 1999). NICE does not however have power to set or modify the price at which a health technology may be supplied to the NHS.	This comment has been superseded by the agreement of a final response scheme between the manufacturer and the Department of Health.

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	It is of course open to the Institute to reject Janssen-Cilag's response scheme if there are sound reasons, based on the clinical and cost effectiveness of bortezomib, for doing so; we do not believe such reasons exist in this case. It is not however within the power of the Institute to devise an alternative response scheme, with associated provisions for when a rebate should be paid by the company and to make recommendations to the NHS on that basis. In this case, the Appraisal Committee appears to have tried to select a "sub-group" of patients from the Janssen-Cilag response scheme; in doing this however it has seemingly failed to consider that it is seeking to define the circumstances when a rebate in respect of the price of bortezomib should be paid by the company. Such a strategy exceeds the powers of the Institute. We would point out that while the Appraisal Committee appears to have taken the view that bortezomib is particularly cost effective in patients who develop an early CR/PR, a scheme which limited bortezomib to such patients would deny access to a group of patients who have achieved a significant clinical outcome, especially when their inclusion delivers a cost per QALY well within the range of agents which have been accepted for use by NICE.	
	1.2 <u>The Importance of Minor Response</u> The Appraisal Committee has expressed concerns about the clinical relevance of achieving an MR at cycle four and whether the inclusion of such patients in the scheme dilutes the survival advantages (and so cost-effectiveness) of bortezomib. These questions were first raised during the clarification step before the Appraisal Committee met to consider the ACD but given the extremely tight deadlines we were unable, at that stage, to provide the requested clinical evidence comparing outcomes for patients who experienced an initial MR with those for patients who initially showed a PR or CR, because the APEX trial data had not previously been analysed in this way. The additional time that has now elapsed has enabled us to commission new analyses using the APEX study 1st relapse data set to explore these issues further. The key points from these new analyses are as follows: 1. With continued treatment, clinical outcomes for patients who are MRs at cycle 4 are similar to those who achieve a CR or PR by cycle 4. 2. Stopping treatment in MRs at cycle 4 reduces the total number of complete responders by 19%. 3. Post hoc analysis suggests that patients who achieve best responses after cycle 4 appear to have longer time to progression than earlier responders.	The Committee has carefully considered the evidence made available on outcomes for minimal responders, and was not persuaded that clinical benefits of bortezomib in minimal responders are comparable with partial and complete responders (see FAD section 4.11). Furthermore, the Committee was not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15).

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	1.2.1 Clinical Outcomes According to Response After Four Cycles. The objective of these analyses was to compare time to progression (TTP) and overall survival (OS) according to level of response at cycle 4. Response was defined as CR, PR, MR or NR (No response) according to the level of improvement in serum M-protein (Table 1). Table 1. Median TTP and Survival In Months According to Response at 4 Cycles (CIC) These new post-hoc analyses demonstrate that: • All 1st relapse responders (CRs, PRs and MRs) have markedly longer median TTP than non-responders. • Differences between CRs and MRs are modest, with a median difference in TTP of 1.4 months (around 6 weeks). This occurs because MR is a valuable clinical outcome in its own right and also because 19% (9/47) of patients who are initially MRs convert to CR or PR after cycle 4 with continued treatment. • Overall survival was not evaluable because median survival has not been reached for responders. However, median survival has been reached for non-responders (22.5 months). These results are also presented below in the form of a Kaplan-Meier analysis, which shows the association between the three response groups (MR, PR or CR at cycle 4) and the clear separation from non-responders. **Figure 1. Kaplan-Meier Analysis of TTP by Responder Group** (CIC)	The Committee noted that the median time to progression for minimal responders lay between non-responders and complete and partial responders but that there was considerable variability in the data (see FAD section 4.11)
	1.2.2 Clinical Relevance of MR In the APEX 1st relapse cohort, around 80% [redacted] of patients who initially achieved an MR improved further with continued treatment. In 19% [redacted] of initial MRs, this conversion occurred post four cycles of treatment. Importantly, there were 31 patients who achieved a complete response in the 1st relapse patient population in the APEX study, of whom 6 were still MRs after 4 cycles of treatment. Based on these data, a response scheme, which curtailed treatment of MRs at cycle 4, would deny 19% (6/31) the opportunity of achieving a complete response. A relevant question to assess the importance of ceasing treatment in these patients is to understand whether there is a difference in outcomes between patients who achieve “later” versus “earlier” response. To investigate this, we have undertaken a further re-analysis of the 1st relapse cohort of	See response above.

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	the APEX study to compare outcomes for patients who achieved a best CR or PR response within the first 4 cycles of treatment compared to those who achieved a best CR or PR response after 4 cycles of treatment. These post-hoc analyses suggest that patients who convert from an initial MR within the first 4 cycles, but then progress to achieve a CR or PR after four cycles have longer TTP's [redacted] than patients who achieve CR or PR within the first 4 cycles [redacted]. Although this was a post hoc analysis, and there are numerical imbalances between the groups, it does provide a strong justification for allowing patients who achieve an initial MR within 4 cycles to continue with their treatment. Table 2: Comparison of Outcomes for "Earlier" and "Later" Best Response (CIC)	
	1.2.3 Summary In summary, the new analysis presented in Table 1 demonstrates that patients who are MRs at cycle 4 have a TTP that is similar to patients who are CRs and PRs at this stage of their treatment (the response scheme decision point). The most obvious differentiation in these data is between MRs and non-responders. It is clear that achieving any form of initial response is the most important predictor of TTP. Table 2 presents new data suggesting that later responders may have longer TTP than early responders. In this analysis, late responders [redacted]. We believe that these data demonstrate that patients who achieve an initial MR at cycle 4 have achieved a valuable clinical outcome. The fact that 19% of patients who are MRs at cycle 4 convert to PRs or CRs means that continued treatment is in the best interests of patients and supports the Janssen-Cilag response scheme. These results also demonstrate that the survival and QALY gains predicted by the model would not be impacted by inclusion of initial MRs; in fact there is evidence of higher TTP rates in patients who achieve a CR/PR best response after cycle 4.	See response above.

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	2. The use of Mayo Clinic Observational Data to model decline following disease progression At section 4.7 of the ACD the Appraisal Committee expresses the view that the results generated by the cost-effectiveness model may over-estimate the cost-effectiveness of bortezomib because of uncertainties associated with use of the Mayo clinic observational data to model decline following disease progression. No explanation for this conclusion is provided in the ACD and Janssen-Cilag believes it is inappropriately pessimistic. As explained in Janssen-Cilag's original submission, the Mayo Clinic observational study assessed the clinical course and outcomes of patients with multiple myeloma who experienced disease relapse following treatment. The baseline patient characteristics for patients in this study were comparable with those who participated in the APEX trial of bortezomib, both in terms of patient demographics and disease characteristics. The data were therefore used in the model provided to NICE both in respect of bortezomib and the comparator, to represent outcomes following disease progression. The Appraisal Committee has provided no explanation for its conclusion that the data from the Mayo Clinic study are uncertain or that use of these data may bias the results of the health economic assessment in favour of bortezomib. In circumstances where the Mayo Clinic data was obtained from patients similar to those who participated in the APEX trial, it is unclear why this might produce bias and, even if bias were to occur, in circumstances where the Mayo Clinic data was used to model both treatment arms, any such bias would affect both treatment arms in the same way after initial progression. In their assessment of the Janssen-Cilag model, the ERG concluded that the model is most sensitive to the cost of bortezomib and TTP. As treatment TTP's are derived from the randomised phase of the APEX trial, these are robust estimates.	The Committee noted the manufacturer's assertion that the inclusion of Mayo data affected only post-progression survival. However, it did not agree since the Mayo data had been used throughout the model and would therefore influence the modelling of both time to progression and overall survival for both bortezomib and HDD arms. (see FAD section 4.7)
	3. **The Appraisal Committee has not considered the positive recommendation for bortezomib, in the context of the factors identified at paragraph 6.2.6.10 of the Guide to the Methods of Technology Appraisal** During the course of the Appeal Hearing, Janssen-Cilag expressed its concern that in considering the appraisal of bortezomib, the Appraisal Committee had not referred to the factors identified at paragraph 6.2.6.10 of the Guide to the Methods of Technology Appraisal. These factors include: • The degree of uncertainty surrounding the calculation of ICERs • The innovative nature of the technology • The particular features of the condition and population receiving the technology and • Where appropriate, the wider societal costs and benefits. We explained why, in our view, bortezomib scored highly on the identified factors and that, if these	The Committee considered the innovative nature of bortezomib, the severity of disease and the alternative treatment options for people at this stage of the disease, but concluded that, on the basis of the evidence currently available, it was not in a position to recommend bortezomib without a rebate

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	were properly considered by the Appraisal Committee, this should favour a positive recommendation. In its decision, the Appeal Panel confirmed that, if the Appraisal Committee "*should decline to recommend bortezomib treatment for use in the NHS, [it] must explain more fully its reasons for failing to recommend such treatment with the first of a new class of drugs that the Committee accepted would prolong, significantly, the life of patients with an incurable disease; and whose incremental cost-effectiveness ratios were within the same ranges as the cost of some treatment it had previously considered to be an effective use of NHS resources*". The wording of the ACD suggests that the Appraisal Committee's rejection of bortezomib for patients following first relapse or for patients following first relapse and when treatment ceases after three cycles if patients fail to respond, is solely based on the Appraisal Committee's concerns regarding uncertainties associated with the cost-effectiveness. We have explained above why we believe the concerns of the Appraisal Committee with respect to this is unwarranted and believe that, despite the Appeal Panel's determination on this point, the rationale underpinning these opinions remains poorly explained. In these circumstances, we believe there is a high requirement for the Appraisal Committee to consider all of the factors listed at paragraph 6.2.6.10 of the Guide to the Methods of Technology Appraisal in the context of the very important benefits associated with bortezomib therapy. **Conclusion** In summary, we believe that, when all relevant evidence is taken into account bortezomib is cost effective when assessed using a standard approach. However, in view of the fact that Janssen-Cilag is committed to ensuring that all eligible patients who could benefit from bortezomib have access to this treatment under a scheme which is cost-effective for the NHS, we have proposed a response scheme which optimally delivers on both of these objectives. New analyses presented here show that the scheme proposed by NICE would deny some patients important clinical benefits associated with continued bortezomib treatments. The Janssen-Cilag response scheme therefore represents a sound basis for guidance to the NHS.	scheme (see FAD 4.13).
Clinical specialist	Thank you for giving me the opportunity to comment on the revised ACD, Bortezomib Monotherapy for Relapsed Multiple Myeloma.	

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	i) Given the constraints of the Appraisal that insists on the consideration of monotherapy only, I consider that all the relevant evidence has been taken into account, but clearly, as I have stated previously, I think that the response rates with combinations including Velcade will be higher than those with single agent Velcade alone. ii) I think that the summaries of the clinical and cost effectiveness of Bortezomib and monotherapy are reasonable interpretations of the evidence, are relevant clinically and allow a consideration of the cost effectiveness of the drug. The concept of a VRS (Velcade Rebate Scheme) is a good idea and I consider the summaries of the cost effectiveness presented in the hearing to be an accurate reflection of the clinical use of this drug. In particular, I would like to stress that in my opinion, if the Rebate Scheme is followed, that the majority of patients will benefit and the small minority of patients who may show signs of a response after 4 cycles, is not a significant clinical consideration. In my own clinical practice, I would be unlikely to wish to consider on going treatment, unless I had seen, what I consider a meaningful clinical response, by this number of cycles. Iii) I consider the provisional recommendations of the Appraisal Committee to be sound and constitute a suitable basis for the preparation of guidance to the NHS. In conversations I have had with the company, they have outlined what sounds like a very 'forgiving strategy' for the use of this Scheme. However, I would like to be sure that the NHS receives firm assertions that the assessment of response will not be punitive, and that over interpretation of paraprotein responses will not be made and used as a way of avoiding a rebate. Similarly, given the wording of the Appraisal, I would like to be reassured that the Rebate Scheme is available for all patients where Bortezomib is used, not only at first relapse. It is also important that the administration underlying the scheme, is functional, and does not impose an excess of work on the pharmacy and clinical staff. I am sure that all of these issues can easily be addressed, but we do need to have reassurance and commitment from the company to make this happen.	Comment noted. Comment noted. Comment noted. Bortezomib is recommended for patients at first relapse only because it is not cost-effective at second and subsequent relapse (see FAD section 3.6 and 4.5)
Joint comments: Royal College of Pathologists, Royal College of Physicians, British Society of	**Do you consider that all of the relevant evidence has been taken into account**? We are satisfied that the Appraisal Committee has considered the evidence available and we are particularly appreciative of the fact that the committee has taken into account the views of people with multiple myeloma , the organisations who represent them, and the clinicians who treat people with myeloma. We understand that the complexity of the disease and the fact that different treatment approaches are	

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Haematology, UK Myeloma Forum	required at different times and for different individuals has made this appraisal particularly challenging. We value the fact that the Appraisal Committee has recognised these factors and taken them into account in their determination. **Do you consider that the summaries of the clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and the implications for the NHS are appropriate**? We note and support the appraisal committee's conclusion that the Apex trial constitutes clear evidence that Bortezomib is more clinically effective than HDD monotherapy. We welcome the Appraisal Committees approach to the manufacturer's suggestion of implementing a response based stopping rule with a rebate for non responders. This will effectively reduce the cost pre QALY and we see this as a creative way of making this effective agent affordable to the NHS and thus available to patients. **Do you consider that the provisional recommendation of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** We welcome then Appraisal Committee's recommendation which if implemented will enable clinicians to use this effective therapy and treat patients appropriately. We note the appraisal committee reluctance to include in the recommendation the group of people whose disease demonstrates minimal response (MR) as has been suggested by the manufacturers. Whilst we acknowledge that as yet evidence that achievement of MR can be shown to be cost effective is not strong, we wish to record that achieving clinical improvement and arrest of progress of disease is beneficial and undoubtedly associated with prolongation of survival. In summary our Professional bodies welcome the Appraisal Committee's recommendation which we believe to constitute a fair and constructive approach to the challenge of making Bortezomib, a major clinical advance , available to patients with Multiple myeloma which would result in improvement both in the quality and duration of their lives.	Comment noted. Comment noted. The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). Furthermore the Committee was not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15)
Joint Patient Interest Group Submission:	Do you consider that all of the relevant evidence has been taken into account? 1.1 As the recommendations stand in the revised ACD, all myeloma patients who are suitable for bortezomib (Velcade) will now get access to this clinically effective treatment. We	1.1. Comment noted.

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Myeloma UK, Cancerbackup and Leukaemia CARE:	absolutely support this principle. 1.2 Whilst we are pleased that this draft recommendation is positive, we remain disappointed that NICE is not able to appraise treatments outside of their licensed indication, even if the indication has fallen behind clinical practice. To consider bortezomib as part of combination therapy would have been more clinically relevant, a point we have argued consistently throughout the appraisal. However, we do recognise this is currently beyond the powers of NICE. 1.3 The Velcade Response Scheme (VRS) was designed by the manufacturer in conjunction with the Department of Health to overcome the cost effectiveness uncertainty of bortezomib. As such we were not involved in discussions about the scheme or its design. In terms of the design of the scheme as set out in the ACD, we accept the Committee's assertion that there is limited evidence regarding the association between magnitude of initial M-protein response and prognosis. However, it is well accepted among treating clinicians that response to treatment should be viewed in the context of each individual patient and that the duration of response is as clinically relevant as the magnitude, especially in the presence of improvement in endorgan damage and resulting quality of life. It therefore may not always be clinically appropriate, ethical or cost effective to deny patients access to a maximum or minimum number of treatment cycles based only on magnitude of response. Our concern is that patients in the minimal responder (MR) group who achieve a smaller magnitude of response at four cycles as measured by M-protein would, with further treatment, achieve a long duration of stable, asymptomatic disease. We therefore consider that the VRS should include MR so as to ensure that all benefiting patients continue to do so and are not prematurely excluded from treatment with this therapy. Do 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 Notwithstanding the points we raise at 1.2 and 1.3 we feel the recommendation is a fair reflection of the evidence and are pleased that bortezomib has been recognised as a clinically effective drug. 2.2 We do however remain disappointed that the Appraisal Committee and the manufacturer were unable to remove the uncertainty around the cost effectiveness of bortezomib without the VRS. Nevertheless we have no doubt that the VRS is implementable and will have little or no impact on resource planning for the NHS.	1.2 Comment noted. 1.3. The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). The Committee was also not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15). 2.1 Comment noted. 2.2. The Committee remained concerned about the uncertainties related to the ICERs without the rebate scheme (see FAD section 4.13).

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	2.3 We applaud the willingness and commitment of the Institute, the Department of Health and the manufacturer to making bortezomib available within the NHS and for creating an innovative solution to ensure that this important treatment can be accessed by patients. Do 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 As the recommendation stands, all patients who are suitable for bortezomib will now get access to it. We absolutely support this principle and welcome that the guidance is applicable to all relapsing myeloma patients. 3.2 However as outlined in point 1.3 we have significant concerns about the appropriateness of ending bortezomib treatment for minimal responders after four cycles, as currently outlined in the VRS, and would urge the Appraisal Committee to reconsider this aspect of the guidance before issuing the Final Appraisal Determination.	2.3 Comment noted. 3.1 Comment noted 3.2. The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). The Committee was also not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15)
DHSSPS NI	**Comments on Bortezomib Monotherapy for Relapsed Multiple Myeloma** I welcome the provisional recommendations of the ACD for Bortezomib. Use of Bortezomib as second line treatment will result in an initial increase in costs in Northern Ireland where it is currently used as a third line treatment. Bortezomib will be used earlier in the course of each patients disease. We now need some estimate of what these costs might be for the myeloma population in N Ireland. I think the “rebate scheme” is a reasonable way to contains costs.	Comment noted.

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Joint comments: Cancer Network Pharmacists Forum, British Oncology Pharmacy Association	We write with regards to the current Appraisal Consultation Document entitled Bortezomib monotherapy for relapsed multiple myeloma and would like to express our concern over particular statements in the "Department of Health summary of the responder scheme" regarding the Velcade Response Scheme (VRS). The British Oncology Pharmacists Association (BOPA) represents 500 individual members across the UK, the majority of whom are oncology pharmacists and the Cancer Network Pharmacists Forum (CNPF) represents Network Pharmacists from all NHS England Cancer Networks which have established a Lead Pharmacist post. In addition BOPA is also listed as one of the consultees for this appraisal. As chairs of these groups we are surprised to hear "The company has consulted with a number of Senior….. pharmacists", that these individuals were "positive towards such a scheme" and that they felt this scheme could be "implemented with no incremental cost to the NHS". We have not had a chance to consult BOPA members, in particular Chief Pharmacists, but early communication from members and discussion at a recent meeting of the CNPF would suggest that this is not the case. Discussion at the last business meeting of the CNPF highlighted that the Network pharmacists are certainly not yet "positive towards such a scheme" and remain to be convinced that "this scheme could be implemented with no incremental cost to the NHS". As senior pharmacists within their Networks the view held so far, and laid out previously by XXXXXXX on our behalf, is that the VRS will have an impact, which remains to be quantified, for already stretched pharmacy departments as Janssen-Cilag will, presumably, want a level of detail to clarify the circumstances under which a claim is made. We know, from experience, that the role of collating this data is likely to fall to oncology pharmacists in Acute or Foundation Trusts and is likely to be time and resource intensive. We agree with XXXXX's assertion that this is not necessarily a "show stopper" for bortezomib alone but we are aware of other similar proposals being considered by DoH (such as sunitinib (Sutent)) which will also require considerable input to manage them, and that this support will more than likely have to come from pharmacy departments. We have already had, informally, early indications from industry that if the VRS is accepted by NICE and the DoH other companies will not be slow in attempting to follow suit and if accepted the situation would quickly become unmanageable. Finally we are also concerned that as part of the VRS scheme "the company will only provide replacement stock or credit for those patients at first relapse who fail to respond to Velcade" rather than "cash-back". We are certain that in the new financial flows of the NHS a PCT would want a refund for their own non-responding patients - if the Trust gets refunded replacement stock or credit that "refund" may not (or certainly won't easily) get back to the original PCT as the vials will almost certainly have to be used in whichever PCT's patients turn up next to avoid wastage. There may be ways around this but again this adds	The Committee noted these concerns but was also aware of the significant reduction in the ICER associated with the rebate scheme and the substantial benefits to patients of the availability of bortezomib delivered in this way, and was reassured by advice from the Department of Health that it considered that the scheme will not impose a disproportionate organisational burden on relevant NHS organisations in England. (see FAD 4.14 and 5.3) The manufacturer has indicated that a cash rebate is possible if this is the preferred option.

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	to the complexity on the ground and may further slow down the uptake of any NICE guidance by Trusts and PCT's. We would like to finish by stating that we fully support any attempt to reduce the price of a therapy to allow it to be used in the relevant patient population but our concern is that the VRS as it stands may slow down uptake of any positive NICE guidance whilst the issues highlighted above are sorted out at a local level. We would also suggest that if the VRS is approved and followed by the proposal and approval of other similar systems for other therapies the situation would quickly become unworkable across the NHS. We would be more than happy to work with the company to find solutions to some of the potential problems with the system as it is currently proposed,	
Cancer Network Pharmacists Group and BOPA.	1. Administration of the VRS within the NHS – [The Department of Health's] comments of the 25th April are noted in particular "We ... believe that it will not impose a disproportionate organisational burden on NHS organisations.." I agree with his comments within the context of this scheme but warn that schemes such as this may be the thin end of the wedge. The VRS will have an impact as Janssen-Cilag will, presumably, want a level of detail to clarify the circumstances under which a claim is made. This will mean someone sitting down and going through the notes and the lab results for the patient. At a rough guess 2 or 3 hours work. Whether building in a cost for this would alter the economics of the scheme I could not say. Most Pharmacy systems work on an average pricing system so any "refund" could not be attributable to an individual patient (or their commissioning PCT). This is not a "show stopper" for bortezomib but we are aware of other similar proposals being considered by DoH (such as sunitinib (Sutent)) which will also require considerable input to manage them. 2. On a clinical / statistical note, I would expect that most clinicians would use bortezomib in combination with another agent, most likely dexamethasone. If one accepts that the response rate from a combination is better than bortezomib monotherapy, the cost / benefit equation of the VRS would be skewed such that Janssen-Cilag will be refunding fewer non-responders. This is quite likely to occur, dexamethasone as a single agent produces a good response rate. The problem with it is that the responses become less and less durable. I am aware that the trial data are not there to calculate an effect exactly but this should be borne in mind in any negotiations.	Comment noted. The Committee is not in a position to take into consideration the use of bortezomib in combination with other drugs because this use of bortezomib is not included in the marketing

Consultee or Commentator	Comment	Institute Response
		authorisation.

Reply received but no comments:

- Royal College of Nursing of the United Kingdom
- Department of Health

Web comments	Comment	Institute Response
NHS Professional 1	Section 1: This appears on the surface to be a sensible way forward. The only concern I have is with regard to the precedence being set for other mediciation in this field and the cost to the service in the future of managing it.	Comment noted.
Patient 2	I nearly died in Nov 2007 because of your rulings. 10 days in hospital got me fit enough to go on the manufacturer''s VIM trial. Now I have another year or two of fit and active life. TERMINAL PATIENTS ARE NOT JUST AN ADMINISTRATIVE STATISTIC! Section 1: This is a VERY VERY poor second option. This was the only option about 2 years ago. Now the common option should be NHS TRIALS with second and third combined chemotherapies to enhance the response. There are so relatively few Multiple Myeloma patients that ALL treatment should be recorded and analysed, probably by a beefed up Myeloma Forum.	Comment noted.
	Section 2: Until doctors can accurately forecast side effects for each patient, the use of this drug should be restricted to patients who have run out of older less invasive treatments. I got a tiny increase in my Thalidomide neurophathy on the second cycle, but got hit hard with neuropathy on the third 80% cycle. It is well worth it to stay alive, and I just take reducing amounts of pain killer as the neurophathy subsides!! Now I can walk a couple of miles without discomfort.	Comment noted.
	Section 3: PLEASE, PLEASE find a way to accept EVERY new drug as manufacturers produce them. Just restrict them to experimentation when safer options no longer work. That way relatively few long lived patients like me get the opportunity to act as guinea pigs for the doctors'' learning curve. I hope I am a useful member of society both during treatment and between relapses, and ''''selfishly'''' I want to live for the CURE.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5).
	Section 4: Bortezomib isn''t an aspirin, to be given out by junior doctors. You base your decision on 560 odd patients, compared with 12,000 patients for Herceptin. The survival of the Myeloma patient is a statistic to be analysed, by the specialist doctors who are learning about these new drugs. It''s an experimental cost, which is why the drug should be funded centrally. To have a PCT Assistant Commissioner tell the patient ''''hard luck, we can''t afford to keep you alive'''' is an utter disgrace for our present ''''third world status'''' NHS. You can have no concept of the stress caused to my family and myself at that time!	The Committee is required to make decisions on the basis of clinical and cost effectiveness.
	Section 5:	Comment noted.

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	Please make you final decision quickly. The PCTs are likely to use the intervening time to let a few more patients die earlier than necessary.	
	Section 6: An absolutely crucial aspect of all Myeloma treatments!	Comment noted.
	Section 7: NICE should not even have to discuss this. Let the doctors get on with experienting to cure ALL the side effects of these drugs. As a terrminal patient, I expect doctors to try out any formally agreed trials approved by their peers, ie. The Myeloma Forum of doctors.	The Department of Health has requested NICE technology appraisal guidance for bortezomib, and the Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness
	Section 8: It seems a bit pointless. The idea of Bortexomib Monotheraphy is already completely out of date. We know that a mixture of drugs gives an improved response. You are recommending spending 25,000 on patients, but refusing them improved treatments with fewer cycles. I only cost the manufacturer around 9000 for my drug (after the PCT used you as an excuse for refusing me treatment).	NICE processes stipulate that the need for a review be assessed at an appropriate time after issuing guidance, and a review is only carried out if new evidence has become available that could potentially change the original recommendations.
NHS Professional 2	Section 1: In my experience Bortezomib is poorly tolerated in patients who have already received several lines of Myeloma therapy (inculding Thalidomide). Many of these patients have had to discontinue Bortezomib therapy after 2-3 cycles owing to unacceptable side effects (even de-escalating dose as per manufacturer"s guidelines). Most of these patients will have had a reduction in their paraprotein and so would not trigger a "refund" in this scheme but will not have obtained any significant clinical benefit from Bortezomib as their Myeloma progresses very rapidly after only a short period of therapy. Has this issue been addressed?	The recommendations are for patients at first relapse only. The costs associated with adverse events were included in the model, but the effect of adverse events on QALYs gained was not explicitly modelled (see FAD 3.6 and 3.7)
	Section 3: Are these refunds going to be "real" or "free" drug?	The manufacturer has proposed a rebate by replacement stock but has indicated that a cash rebate is possible if this is the

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		preferred option.
Patient 2	I am a myeloma patient who has relapsd following a bone marrow transplant. Section 1: I welcome the access to bortezomib treatment that this would bring. As a patient I felt unreasonably excluded from access under the original NICE decision. The financial arrangement is really outside my area of competence but sounds a resonable and novel suggestion. (Some reference in the document to the literature on the use of serum M protein as a measure for cancer burden would be helpful).	Comment noted. Reference to the use of M protein as a measure for cancer burden can be found in the manufacturer's submission and is discussed in the FAD sections 4.10 and 4.11.
	Section 2: The price information is not that helpful to me as a patient- really I want to know what the cost would be to me or my PCT. I also don''t see why the rebate arrangements are quoted for a four cycle stopping rule, but the price information for three and eight.	The text of the FAD has been amended for clarity (see FAD 2.3)
	Section 3: The manufacturer''s submission draws attention to the additional factors, taken into account by NICE in the initial appraisal, where the cost per QALY is over 20,000. Janssen-Cilag clearly found the way in which these factors were considered rather obscure, or at least ill-described. I strongly agree with them on this.	The Committee considered the innovative nature of bortezomib and the severity of disease and the alternative treatment options for people at this stage of the disease but concluded that, on the basis of the evidence currently available, it was not in a position to recommend bortezomib without a rebate scheme (see FAD 4.13).
	Section 4: There is a risk that the detailed numbers for cost-effectiveness are pushed beyond the basic clinical data that led to them- one then has ""data"" generated by the model and without a degree of scepticism directed at the modelling itself there is a false sense of objective information. Nonetheless the overall conclusion seems reasonable to me.	Comment noted.
	Section 5: The consistency of implementation is regularly an issue in the NHS at present. I doubt that bortezomib will be different and I personally think differences in implementation are unfair and unjust.	Comment noted.
	Section 6: I agree. Section 7: No comment. Section 8: I would have thought it could be sooner than three years- especially given the rate of development of treatments.	The need for a review will be assessed at an appropriate time after issuing guidance, and a review is only carried out if new evidence has

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		become available that could potentially change the original recommendations.
NHS Professional 3	I am a public health consultant and I am on the panel that advises the pct on the funding of non-contract treatments. Section 1: I do not support this recommendation for a number of reasons. I will summarise them briefly. 1. This is likely to be unworkable in practice for various. Once a patient is on a treatment it will be extremely difficult for clinicians to stop it if there is any response at all. It will be even harder than not starting treatment in the first place. Secondly, oncologists and haematologists have, largely, been unsympathetic to PCTs trying to manage their budgets. There will be no willingness on the part of most of them to alert pcts to cases of inadequate response. You could say that PCTs can build it into commissioning arrangements and in theory they can, but it will all require that the pct is very active in following cases up, and this will be an extremely difficult process and will involve a lot of conflict and also time. 2. This could set a trend by which many other expensive drugs will seek to market themselves and force the hand of the NHS. 3. Since every licenced drug works for some it could signal the end of NICEs ability to say no to any new drug, however un-cost effective and removes any incentive to price moderately. NICE is risking major self-disempowerment.	The Committee was persuaded by the clinical specialist that response can be assessed in an appropriate time frame to allow implementation of a stopping rule and that this approach is current practice in the UK (See FAD section 4.9) Furthermore, the Committee noted the concerns about the cost of implementing and administering the rebate scheme. However, the Committee agreed that the substantial benefits to patients of the availability of bortezomib delivered in this way would not persuade them to alter their view on the recommendations in the guidance section (see FAD 4.14)
	Section 2: 1. this drug cannot be considered in isolation. Very many drugs now comning on stream put the biological brakes on cancer (or other conditions) without offering any hope of cure or even long term remission. All are heavily marketed and are priced either just below the cost effectiveness threshold or a bit above to push the envelope. This will set a major precedent that everyone should have the chance to get everything as some will surely respond. Secondly, the 20-30k threshold is not a natural law but based on what is affordable to the NHS. If more and more treatments are costed at this level it then it all becomes unaffordable at some point and then more cost effective but ""un-NICED"" services will be cut instead. 2. Everyone now has to ""fight"" cancer, and increasingly death is seen as a failure of medical treatment. It seems that the ability of clinicians to explain the real benefits and costs in qol to patients is diminishing and no cost is too great for a	Comment noted. Comment noted.

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	few months life extension. This is why companies emphasise LYG so much. Eg. I have had a request for Bortozomib and HDD for a patient who has actually had to stop Dex in the past, and who has had cord-compression.	
	Section 3: In every case that I have ever seem the manufacturers submissions are more favourable than the independent ones. I"m afraid that manufacturers modelling, and increasingly even the basic trials that are done, owe more to marketing departments than to any concept of disinterested science. The degradation of the evidence base itself is becoming deeply disturbing. I could expand the methods used to distort and mask the reality, but I assume that they are well known to NICE. One thing that is happening repeatedly is that small trials are truncated before final results come through on the bases of some small early improvement rendering it ""unethical to continue the trial"". These improvements could easily be blips in these often small phase two trials, and yet once a trial is cut off there is then no incentive for the manufacturer to do any more research when its money is then better spent on the marketing push. I worry that we are starting to load the dice so much in favour of new drugs in this and other ways that we are seriously in danger of pushing drugs through that would actually turn out to be almost useless if a proper range of trials were done. This is unethical too.	The Committee is aware of the potential biases in the clinical evidence and the uncertainties associated with the economic modelling and takes this into account in it decision making.
	Section 4: 1. I dont necessarily agree with 4.13. If you are using manufacturers estimates of 20K I would have thought it perfectly likely that the real ICER could be well above 30k based on many other manuracturer/independent ratios in different appraisals. Also remember that 20-30 k is meant to be the threshold that NICE use and not simply 30K. 2. You assume in your modelling a perfect rebate scheme with all costs recovered which is very unlikely.	1. In addition to cost effectiveness, the Committee takes into consideration the clinical need, nature of the disease, availability of alternative treatments and the innovative nature of the technology (see Guide to the Methods of Technology Appraisal (Available from URL http://www.nice.org.uk/page.aspx?o=201974). 2. The Committee noted the concerns about the cost of implementing and administering the rebate scheme. However, the Committee agreed that the substantial benefits to patients of the availability of bortezomib delivered in this way would not persuade

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		them to alter their view on the recommendations in the guidance section (see FAD 4.14)
	3. You clearly demonstrate that the evidence regarding minimal responders is so muddy that clinicians and patients will fight all the way to keep on treatment. Some policies are intrinsically unworkable and this seems to fall into that category. Every such case will become a cause celebre.	3. The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). The Committee was also not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15)
	4. You seem to be taking the first relapse condition off completely and replacing it with a response condition. Therefore it seems that this can now be used in first or subsequant relapses. Have the actual cost and affordability implications been modelled? If it is used as monotherapy in first relapse can it then be used with HDD in subsequent relapses?	4. The recent modelling has been provided for patients at first relapse and the recommendations are for patients at first relapse. The FAD has been amended for clarity.
	Section 5: Lots more work for PCTs. More conflict between commissioners, clinicians and patients. There is repeated mention of a rebate, but is this in real money, or a Janssen credit note or a Velcade credit note? There is a big difference in utility and opportunity cost rebate between the first option and the other two. If it is a velcade credit note that is very worrying as it means that there really very little risk to the manufacturers at all in pursuing this precedent with other similar offers. It would be even harder for a pct to withdraw treatment from a minimal responder when it had credit notes waiting to be used.	The manufacturer has proposed a rebate by replacement stock but has indicated that a cash rebate is possible if this is the preferred option.
	Section 6: Granting this drug approval is a one way process. If further research demonstrates that NICE have been too	NICE processes stipulate that the need for a review be

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	lenient, or demonstrates no imporvement in long term prognosis, the deed is done and NICE will never be able to tighten up the rules or withdraw the drug. Of course if it proves more effective and the cost effectivenerss increases that would be a good thing.	assessed at an appropriate time after issuing guidance, and a review is only carried out if new evidence has become available that could potentially change the original recommendations.
	Section 7: The issue of NICE in relation to unlicenced drugs is becoming increasingly important. I particularly notice it regarding Lucentis / Avastin and the unwarranted primacy of Alimta over a large number of other equally effective (or ineffective) and far cheaper more traditional but unlicenced chemotherapy agents for mesothelioma.	Comment noted.
	Section 8: As this arena gets more and more charged any tiny change n the evidence based will take on major significance. I have already been informed by a barrister acting for an appellant that the nice guidence on cetuximab is ""past its sell by date"" and it is barely off the press. I don''t think that there is much that you can do about it but it is an issue that will increasingly occur. the government needs to clearly support the principle that nice guidance lasts and is to be respected until review date unless something comes along that is so significant that an interim policy change is made by nice or someone else.	Comment noted.
Patient 3	Section 1: I am a Myeloma sufferer of over 5 years who has had C-VAMP, stem cell transplant, thalidomide and PAD 14 months ago. My Paraprotien is now undetectable due to Velcade. In fact I may not be here today if it was not for Velcade. I have worked for the NHS for over 27 years and understand health care economics. Velcade is the first new clinically effective treatment in Myeloma for decades, and the entire Myeloma community has been campaigning for access to it for over 3 years. It has been demonstrated in recent trials to offer a significant extension of time to disease progression and increased survival for patients who relapse. NICE should conclude that Velcade be available as a treatment option at first relapse as per the recently published British Committee for Standards in Haematology position statement. Velcade will deprive patients of an effective, licensed therapy. I applaud the drug company for their innovative response scheme. NICE now want to unite with the drug company to ensure this preliminary positive decision is final. Also there should be no discrimination of any patients. NICE have said they will pay for the velcade treatment of those patients that do NOT respond to treatment. Please lets not argue over the issue of partial response. This is a breakthrough for the NHS; embrace it instead of trying to squeeze the drug company a little more.	Comment noted.
Carer 1	Section 1: I am a carer for Marie Morton (one of the velcade three) a patient with multiple myeloma, she is on C D T theropy and will require velcade at her next relapse Velcade has given her the will to carry on with this treatment, which makes her very ill indeed please give us hope for the future GIVE US VELCADE!!!!	Comment noted.
Carer 2	Section 1: I support Myeloma UKs main points on the new Velcade recommendation which are available on their	Comments noted.

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	website including the following. 1. As the recommendation stands, all myeloma patients who are suitable for Velcade will now get access to it.We absolutely support this principle. 2. Whilst we are pleased that this draft recommendation is positive, we remain disappointed that NICE are not able to appraise treatments outside of their licensed indication, even if the indication has fallen behind clinical practice. To consider Velcade as part of combination therapy would have been more clinically relevant, a point we have argued consistently throughout the appraisal.However, we do recognise this is beyond the powers of NICE at this time. 3. We were not involved in the discussions or design of the Velcade Response Scheme but it is our role as patient interest groups to comment on the potential impact of the scheme on patients.	
	Section 4: It is well accepted among doctors that response to treatment should be viewed in the context of each individual patient.It therefore may not always be clinically correct, ethical or cost effective to deny patients access to a maximum or minimum number of treatment cycles based only on a level of paraprotein response. We consider that the Velcade Response Scheme should include the minimal responder group of patients so as to ensure that all benefiting patients continue to do so and do not miss out. 4. Notwithstanding the point we raise in point 3, we feel the recommendation is a fair reflection of the evidence and are pleased that Velcade has been recognised as a clinically effective drug. 5. We applaud the willingness and commitment of the Institute, the Department of Health and the manufacturer to making Velcade available and for creating an innovative solution to ensure that this important treatment can be made available to patients. 6. As the recommendation stands, all patients who are suitable for Velcade will now get access to it.We absolutely support this principle and welcome that the guidance is applicable to all relapsing myeloma patients.	The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). The Committee was also not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15).
	Section 8: There should be the option to consider a review before this date if a substantial body of evidence becomes available regarding use of this drug in tandem with others, or that other patterns of use. If the funding (& rebate) arrangements with the manufacturer broke down for any reason there needs to be a prompt review to ensure that this treatment still remains available.	A review of NICE guidance can be carried out once new evidence has become available that could potentially change the original recommendations.
Patient 4	Section 1: I support this recommendation and am pleased that common sense has allowed myeloma patients to receive this innovative drug as part of their journey.	Comment noted.
	Section 2: I support this recommendation as 1. above.	Comment noted.
	Section 3: Thanks to Jensen-Cilag"s proposal patients can now have this drug. I am concerned as to the cut-off points	The Department of Health has requested NICE

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	between "success" and "failure" in the treatment as no two patients are the same in their response. This needs to be tailored to meet individual needs and left in the hands of the doctors/patients rather than a standard cut-off point.	technology appraisal guidance for bortezomib, and the Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness.
	Section 4: As a recipient of Velcade 2 years ago I have had 18 months of remission living a full and active life. There is no doubt as to its efficacy and its availability to those who need it justifies the fight to obtain it.	Comment noted.
	Section 5: I support the recommendations made	Comment noted.
	Section 6: I support the recommendation. Velcade will I beieve stand up to any further research on its efficacy through patient groups and analysis. The more the drug is used the more research can be carried out. This would not have been possible without the intervention of Jensen-Cilag in making their proposal and thanks to them patients now have the opportunity of a longer and better quality of life. Something that NICE previously wanted to deny us.	Comment noted.
Patient 5	Section 1: The acceptance of the drug for use as a treatment is welcomed. However, I question the lack of flexibility for clinical judgement particularly if the reduction in M-protein is approaching 50% after four treatments and is still on downward trend.	To aid implementation, technology appraisals need to give unambiguous and clear recommendations. However, NICE guidance does not override the individual clinician's responsibility to make decisions appropriate to the circumstances of the individual patient.
	Section 6: Research should include use with other drugs, as is general current practice	Comment noted.
	Section 8: In view of the element of doubt in the evidence expressed by NICE, and the recommendation for further research, an earlier interim review should be carried out in 2009.	A review of NICE guidance can be carried out once new evidence has become available that could potentially change the original recommendations.
Patient 6	Section 1. As the recommendation stands, all myeloma patients who are suitable for Velcade will now get access to	1/2 Comment noted.

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	it.We absolutely support this principle. 2. Whilst we are pleased that this draft recommendation is positive, we remain disappointed that NICE are not able to appraise treatments outside of their licensed indication, even if the indication has fallen behind clinical practice. To consider Velcade as part of combination therapy would have been more clinically relevant, a point we have argued consistently throughout the appraisal.However, we do recognise this is beyond the powers of NICE at this time. 3. We were not involved in the discussions or design of the Velcade Response Scheme but it is our role as patient interest groups to comment on the potential impact of the scheme on patients. It is well accepted among doctors that response to treatment should be viewed in the context of each individual patient.It therefore may not always be clinically correct, ethical or cost effective to deny patients access to a maximum or minimum number of treatment cycles based only on a level of paraprotein response. We consider that the Velcade Response Scheme should include the minimal responder group of patients so as to ensure that all benefiting patients continue to do so and do not miss out. 4. Notwithstanding the point we raise in point 3, we feel the recommendation is a fair reflection of the evidence and are pleased that Velcade has been recognised as a clinically effective drug. 5. We applaud the willingness and commitment of the Institute, the Department of Health and the manufacturer to making Velcade available and for creating an innovative solution to ensure that this important treatment can be made available to patients. 6. As the recommendation stands, all patients who are suitable for Velcade will now get access to it.We absolutely support this principle and welcome that the guidance is applicable to all relapsing myeloma patients.We therefore consider, notwithstanding our point 3, this to be appropriate guidance for the NHS.	3. The Committee has carefully considered the evidence available on outcomes for minimal responders, and was not persuaded that the clinical benefits of bortezomib for minimal responders are comparable with those for partial and complete responders (see FAD section 4.11). The Committee was also not persuaded that adding minimal responders would constitute a cost-effective approach (see FAD section 4.15). 4-6. Comment noted.
NHS Professional 4	Section 1: NICE is setting a major precedent. The introduction of a risk-sharing scheme of this nature is something that demands wider consultation on when and how such schemes might operate, be evaluated and performance managed. PCTs bear the burden of challenges on NICE decisions and there needs to be proper consultation with PCTs about this proposal. The ACD does not show that additional costs of operating and monitoring the risk sharing scheme have been fully incorporated into the cost effectiveness analysis. It is unclear whether the proposed scheme will collect data to validate the assumptions required to make Velcade cost effective within the proposed arrangement.	The Committee noted the concerns about the cost of implementing and administering the rebate scheme. However, the Committee agreed that the substantial benefits to patients of the availability of bortezomib delivered in this way would not persuade them to alter their view on the recommendations in the guidance section (see FAD 4.14)