COMMENTS ON THE APPRAISAL CONSULTATION DOCUMENT (ACD): BORTEZOMIB FOR RELAPSED MULTIPLE MYELOMA

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.

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. The approach of the Appraisal Committee to Janssen-Cilag's response scheme

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.

1.1 NICE has sought to modify the Janssen-Cilag Response Scheme

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.

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 The Importance of Minor Response

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

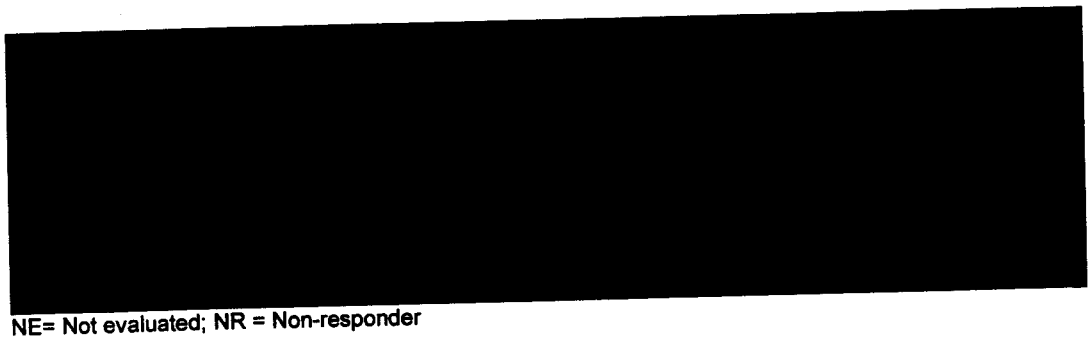
had not previously been analysed in this way. The additional time that has now elapsed has enabled us to commission new analyses using the APEX study 1st relapse data set to explore these issues further. The key points from these new analyses are as follows:

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.

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



NE= Not evaluated; NR = Non-responder

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

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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 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

[redacted]

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.

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.

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 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.