Janssen-Cilag Ltd

Issues for Clarification

Janssen-Cilag appreciates the opportunity to clarify the issues that have arisen following our evidence submission.

A number of the questions concern the cost-effectiveness impact of defining response in the VRS including or excluding minimal response (MR) patients. We wish to make it clear that these analyses are not relevant to the Appraisal Committee's decision-making because the VRS scheme is offered to the NHS only under the terms that have already been presented. Therefore within the VRS, patients achieving an MR would be defined as a responder.

It would not be appropriate to define response only as a PR+CR because it is clinically relevant for patients to achieve an initial MR within the first four cycles of treatment. The APEX data shows that around a third of patients who achieve an MR within the first four cycles go on to achieve even better levels of response with continued VELCADE treatment. As a consequence, the company would not be willing to administer a scheme that would cause patients who were benefiting to be withdrawn from treatment when the cost per QALY of VELCADE within the VRS is below £30,000. Our analyses show that the VRS reduces the cost per QALY by around £5,000 to £7,000 compared to no-rebate stopping rule scenarios.

MR was not part of the response scheme presented in our written appeal document, although it is fair to say that the detail of the VRS was never discussed at the Appeal Hearing. This situation has occurred because we were at an early stage of development at the point that we submitted our written appeal documentation. The scheme has evolved over time as we have engaged with clinicians, pharmacists, other stakeholders [redacted].

Finally, we note that most of the correspondence has focused on the VRS, assumingly because the other scenarios are clearly presented. However, we would like to be assured that the Appraisal Committee will give due consideration to all scenarios requested by the Appeal Panel and not just the response scheme. This is especially important given that the original cost per QALY of £33,500 was acknowledged to be of a similar range to other previously approved NICE technologies, especially when the clear survival benefits of the treatment and the unmet need of this population are considered. The Appeal Panel concluded that:

The Appraisal Committee, if it should decline to recommend bortezomib treatment for use in the NHS, must explain more fully its reasons for failing to recommend such treatment with the first of a new class of agents that 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 treatments it had previously considered to be an effective use of NHS resources****. The factors listed above give guidance as to the issues, which should be addressed when considering this.*

1. Minimal response

A. Please report the outcomes (time to disease progression, overall survival, response rates) from the APEX study for the MR group, and for the CR+PR+MR group.

We have discussed this request with the statistician who worked on the APEX trial. Their advice is that the Minimal Response (MR) group of 1st relapse patients in the APEX trial is too small to allow any meaningful analysis of time to progression (TTP) and overall survival (OS). However, the clinical relevance of an initial MR is illustrated below - patients who have an initial MR frequently going on to achieve PRs or CRs with continuing treatment.

B. Please explain how any changes in time to disease progression and time from relapse to death that might be associated with including MR in the response criterion have been taken account of in the model?

The economic model is based on two health states: (1) time from initiation of treatment to time to progression (TTP) (2) time from progression to death. The duration in the first health state is estimated using Kaplan-Meier (KM) methods. The duration in the second health state is estimated as the difference in overall survival (OS), again using KM methods and TTP. In our modelling work, response rates are not used to determine the duration in these health states.

All stopping rule scenarios are based on the original model, which provided a 1st relapse cost per QALY of £38,064. In applying a stopping rule, it is important to compute the effect of the stopping rule on two components: (a) savings that stem from reduction in Velcade costs among patients who fail to respond by the stopping cycle and (b) reduction in overall survival that stems from failing to achieve a response by the stopping cycle. Details of the methodology of reduction in OS are provided in the answer to question 2.

Since the model was constructed as a two health state transition model and not as a responder model, specifically including or excluding MR patients would require a differently structured model. In order to avoid this whilst addressing the need to run stopping rule scenarios, we included the impact of responder / non-responders in the calculation of reduction in OS (see below).

2. Calculation of the reduction in QALY gain resulting from the up-to-3 and up-to-4 cycle stopping rules

A. Please explain how the %reduction in overall survival is calculated

B. Please explain if this % reduction was separately calculated for the CR+PR+MR analyses

C. Please explain how the expected increase in rate of progression from response to relapse has been calculated in the model

In the following section, the methodology to calculate the reduction in survival associated with 3 and 4 cycle stopping rules is explained. The percentage reduction for CR+PR and CR+PR+MR is calculated separately. The results presented in the following sections are used in the "Stopping rule & VRS parameter sheet" of the Excel based model already submitted to NICE.

Stopping Rule: Percent reduction in Velcade overall survival

Let pR_i denote the probability of response by the ith cycle *given* the overall probability of response. For example, with CR+PR+MR response using EBMT criterion, 85.9% of responders had their response within the first three cycles. The percent reduction in net gain in overall survival between Velcade and HDD, rOS_gain_i, is assumed to be equal to 1 minus the probability of response by the ith cycles, equal to $1 - pR_i$. With this assumption, 14.1% of responders after cycle 3 will not continue treatment, and thus will not achieve a response with a 3-cycle stopping rule. It is presumed that these patients will have same overall survival as patients who received HDD; the assumption being that the survival benefit of Velcade is directly related to achieving a response.

The next step involves computing the percent reduction in Velcade overall survival associated with the stopping rule at the ith cycle, rOS_i. Let **OS_V** denote mean overall survival with Velcade if the patient is treated according to trial (i.e., no stopping rule), equal to 37.3 months (Section 2.1, Table 4 of the resubmission document). Let **OS_HDD** denote mean overall survival with HDD if the patient is treated according to the trial (i.e. no stopping rule), equal to 25.8 months (Section 2.1, Table 4 of the resubmission document). The difference is equal to net survival gain associated with Velcade compared with HDD, **k** = **OS_V** minus **OS_HDD**, equal to 11.5 months.

The following equation shows the relationship among these parameters:

$$\mathrm{OS\_V} \times (1 - rOS_i) - \mathrm{OS\_HDD} = \mathrm{k} \times (1 - rOS\_gain_i) .$$

The parameters shown in bold are constant, regardless of cycle i, and have been estimated based on the APEX trial without a stopping rule. rOS_i is computed by rearranging terms in the previous equation:

$$rOS_i = 1 - \frac{k \times (1 - rOS\_gain_i) + OS\_HDD}{OS\_V}$$

The table below shows percent reduction in Velcade OS by response criterion, response level, and number of cycle stopping rule.

Scenario	Response criterion	Response level	VRS cycles	pR_i	rOS_gain_i	rOS_V_i
1	EBMT	CR+PR	3	[redacted]	[redacted]	[redacted]
2			4	[redacted]	[redacted]	[redacted]
3		CR+PR+MR	3	[redacted]	[redacted]	[redacted]
4			4	[redacted]	[redacted]	[redacted]
5	M-protein	CR+PR	3	[redacted]	[redacted]	[redacted]
6			4	[redacted]	[redacted]	[redacted]
7		CR+PR+MR	3	[redacted]	[redacted]	[redacted]
8			4	[redacted]	[redacted]	[redacted]

pR_i — probability of response by cycle i if a responder. rOS_gain_i — percent reduction in net gain in overall survival associated with implementing a stopping rule at the ith cycle. rOS_i — percent reduction in Velcade survival associated with implementing a stopping rule at the ith cycle.

A stopping rule at cycle 3 will reduce OS with Velcade more than a stopping rule at cycle 4.

3. Serum M protein

A. Please define and explain the difference between the initial M-protein response and the best M-protein response in Table 12?

The initial M-protein analysis shows the number of patients who have a first (initial) response at each cycle. The response is defined as an MR, PR or CR. Best response shows the greatest level of response achieved at any point during the trial. Where patients improve with continuing treatment, initial and best response will occur at different cycles.

Importantly, comparing the two columns it is clear that patients who achieve an initial response can and frequently do go on to achieve higher levels of response with continued treatment. In fact 32% of patients who had an initial MR by cycle 4 went on to achieve CRs or PRs with further cycles of treatment. The majority of these patients - 24% of all patients who had an initial MR by cycle 4 - went on to achieve a CR. This clearly shows that achieving a MR within the first four cycles is clinically relevant and frequently is the prelude to further improvements in response in later cycles.

In PART 3 of our submission we use initial response to define stopping rules as it is likely to be the more representative data in this pragmatic analysis. Treating clinicians will only know whether a patient has had a response or not at that point in their treatment and will not know whether it represented their best response.

B. In table 12, there are a total of 94 patients at first relapse with serum M protein measurements – what proportion of patients measured with EBMT does this represent and if it was not measured in some patients. Please give reasons.

EBMT was assessed for all patients in the dataset. Therefore, both analyses were derived from the same patient population (n=128). However, more patients were classified as responders using the serum M-protein definition of response than the more rigorous EBMT criteria. Serum M-protein is one of the components of the EBMT response criteria.

4. For each set of the sensitivity analyses (that is, for the current tables 7, 10, 15 and 17):

A. Please table the costs and QALYs for each of the options together with an incremental analysis

B. Please provide results of deterministic and if possible probabilistic analysis

The following Table provides a summary of scenarios as requested.

Table: Summary of Cost-Effectiveness Results Across Scenarios

Scenario	**CR+PR***			**CR+PR+MR**		
EBMT	**Inc. Cost**	**Inc QALY Months**	**ICER (PSA)**	**Inc. Cost**	**Inc. QALY Months**	**ICER (PSA)**
3-cycle stopping Rule	£20,896	7.5	£33, 515 (£28,385-£44,284)	£22,207	7.7	£34,599 (£29,734-£44,530)
3-cycle stopping Rule + VRS	£16,588	7.5	£26,605 (£22,392-£35135)	£18,030	7.7	£28,091 (£24,117-£36,230)
4-cycle stopping Rule	£23,340	8.2	£34,359 (£29,834-£44,349))	£24,161	8.2	£35,568 (£30,653-£45,131)
4-cycle stopping Rule + VRS	£17,153	8.2	£25,252 (£22,121-£32,295)	£18,335	8.2	£26,991 (£23,608-£34,850)
M-Protein Initial				**Inc. Cost**	**Inc. QALY months**	**ICER (PSA)**
3-cycle stopping Rule	N/A	N/A	N/A	£21,733	8.2	£31,994 (£27,406-£40,977)
3-cycle stopping Rule + VRS	N/A	N/A	N/A	£19,177	8.2	£28,231 (£24,275-£35,903)
4-cycle stopping Rule	N/A	N/A	N/A	£22,570	8.4	£32,316 (£28,709-£40,790)
4-cycle stopping Rule + VRS	N/A	N/A	N/A	£19,145	8.4	£27,417 (£23,269-£35,039)

**Scenarios that use a CP+PR definition of response within the VRS are not relevant as they are outside of the terms of the proposed scheme. These analyses are provided for the EBMT response definition simply to allow comparison to the no-rebate stopping rule analysis that was previously presented to NICE to VRS using an identical set of assumptions so that the impact of the rebate on the ICER can be compared.*

C. It has been suggested that a full incremental analysis, including exploration of uncertainty, comparing all strategies based on combinations of inclusion of minimal responders, number of cycles, response measure,

and rebate/no rebate would be very helpful in considering the cost effectiveness of the response scheme. Please provide these analyses.

As discussed with the NICE team, the table presented above provides the data necessary to understand this. We would reiterate that a CR+PR definition of response is outside of the terms of the proposed VRS.

5. Please explain how the implications of providing replacement stock and credit rather than refund of cash to the NHS have been taken into account in cost-effectiveness modelling.

The options of rebating by either replacement stock or credit note were developed following consultation with NHS staff (listed below). The guiding principle was for the rebate to follow as closely as possible the point of treatment within the NHS. For hospitals with multiple patients being treated with Velcade there may be a preference for replacement stock, however, some hospitals will have fewer patients treated with Velcade and therefore may prefer the option of a credit note. A credit note balance can be requested as a cash payment at anytime by the hospital.

Given the option of a credit note or cash refund, there is a clear preference for credit notes within the NHS, as these are easier to track and administrate than cheque refunds. Credit notes are expected to be used within a month (across any Janssen-Cilag products). The company has recently confirmed this preference, checking with administrative functions in 10 NHS hospitals that have recently ordered Velcade. In this survey, 80% said that they would prefer a credit note, 20% replacement stock with none stating a preference for a cash refund.

We do not believe that there is an opportunity cost for the NHS associated with replacement stock unless the particular PCT were only to fund one patient during the financial year and in that instance a cash rebate can be requested by the PCT if preferred. In other situations the PCT would benefit from replacement stock, as the initial course of treatment for the next patient would be started without any additional outlay.

6. Please provide the names of physicians and pharmacists who have been consulted during the development of the Velcade Response Scheme.

7. Please clarify the meaning of 'up to four' and 'up to three' cycles: page 8 of the report says, 'however, we would require patients to receive four cycles in order to make a claim under the VRS'
A. Is this correct?

Thank you for bringing this to our attention. We can confirm that there is a typographical error in this sentence, which should read:

We have used "up to four cycles" as the stopping point because clinicians indicate that they would wish to have the option of continuing for a fourth cycle in some non-responders. However, we would ***not*** *require patients to receive four cycles in order to make a claim under the VRS.*

We would therefore rebate/replace VELCADE costs for those patients who received <u>at least</u> (up to) four cycles of treatment.

B. If the intention is up to four cycles, would that include replacement of stock or credit for non-responders, would this include for those who have experienced adverse reactions/intolerant of the drug?

The scheme is offered on the basis of response. Therefore, patients who receive up to four cycles of treatment and who did not achieve a response would be eligible for a rebate under the VRS. If the patient failed to achieve a response because treatment was stopped for adverse events, they would be eligible for a rebate. However, if they achieved a response and suffered adverse events then they would have been deemed to benefit from treatment and the NHS would pay in this circumstance.

8. For part 3 of your document, please provide the results for both CR+PR+MR and CR+PR (tables 15 and 17).

These analyses are not relevant to the Appraisal Committee's decision-making because the VRS scheme is offered to the NHS only under the terms that have already been presented.