Correspondence following document received from Janssen-Cilag on 27 04 07, 'Issues for clarification'

A. Email accompanying documents from Janssen-Cilag 03 07 05: Attached documents:

1. Comparison of cost effectiveness results using APEX trial's full data set and 1 prior line of therapy data only
2. Table with percentage overall survival reduction in total APEX sample and 1-prior therapy; statements regarding full incremental analysis and effect of adding MR to response TTP

Dear All,

Please find attached further analyses as requested. As I am out of the office tomorrow could you please direct any questions to Ravinder.

One other point I wanted to raise in interpreting these analyses relates to whether the results have face validity.

If you consider that £38K which directly uses the APEX 1st relapse data is a robust estimate, and that around 90+% of patients who respond do so within 4 cycles it makes sense that continuing treatment in non-responders for the full 8 cycles will add mainly cost for little additional benefits. This gives the original stopping rule results of around £33K. It also makes sense therefore if you simply take out the costs of those non-responders, then the ICER will also fall as essentially the cost of VELCADE drops. I hope this makes sense to you.

Kind Regards

Martin

B. Email with further clarification on point 8. of 'Issues for clarification', Janssen-Cilag received 27 04 07

Dear All,

Following our discussion just now, I wanted to clarify the following point which as you pointed out is still not 100% clear. I can confirm that the text of the paragraph below is correct.

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.*

Under the VRS we would rebate patients who had failed to respond and who had received up to and including 4 complete cycles of treatment.

For example, if a patient received only one cycle before stopping treatment (perhaps due to side-effects) and then failed to respond to treatment, we would rebate the cost of that cycle.

Please accept my apologies for any confusion.

Kind Regards

Martin

C. Email sent to Janssen Cilag 03 05 07

Martin,

This is not a formal request for clarification but I've jotted below a couple of the queries we have – just thought would email as a heads up in case you or Ravinder have a chance to look at it before we speak.

1. Reduction in OS in Velcade arm:
    a. Is it possible to have data from which pRi in table on page 4 of clarification document derived?
    b. For scenarios 5 to 7 in that table, we have not been able to replicate the pRi's from Table 12 of the resubmission document – is there another source of data?
    c. Why does original model have [redacted]% whereas new model has [redacted]% reduction in overall survival in bortezomib arm with 3-cycle stopping rule on EMBT CR+PR?
2. Conversion of initial serum M moderate response to CR or PR best response: is it possible to have data from which the 32% and 24% on page 4 were derived?

Data from Table on page 4 in clarification letter								
Scenario	Response criterion		Response level	VRS cycles	pR_i	**total responders in table 12**	**responders**	**our pRi**
5		M-protein	CR+PR	3	[redacted]	[redacted]	[redacted]	[redacted]
6				4	[redacted]	[redacted]	[redacted]	[redacted]
7			CR+PR+MR	3	[redacted]	[redacted]	[redacted]	[redacted]
8				4	[redacted]	[redacted]	[redacted]	[redacted]

Best wishes,
Helen