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Dear [redacted]

Re: Single Technology Appraisal – Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT)

The Evidence Review Group (Southampton Health Technology Assessment Centre) and the technical team at NICE have now had an opportunity to take a look at submission received on the 12th March 2013 by Janssen-Cilag. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 12th April 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Christian Griffiths – Technical Lead (christian.griffiths@nice.org.uk) Any procedural questions should be addressed to Lori Farrar – Project Manager (lori.farrar@nice.org.uk in the first instance.

Yours sincerely

[redacted] – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

General

A1. The references supplied separately from the submission (on compact disc) contained 215 of 220 references – references 37, 85, 126, 163 & 216 were not included. Please could you supply these?

Literature searching

A2. Were any searches for ongoing trials carried out? If so, please supply details of what sources were searched, dates and studies identified.

Clinical effectiveness

A3. The last box in the flow diagram in figure 3, page 45, reports 53 studies, including 15 RCTs – please clarify whether the remaining 38 studies were non-RCTs.

A4. Table 16, page 51-52: the submission reports safety as an 'other endpoint' for the PETHEMA trial whilst the journal publication reports it as a secondary outcome; also, the submission reports a median duration of follow-up of 35.9 months whilst the publication reports 35.2 months. Please clarify these discrepancies.

A5. **Priority question.** We note that the submission identifies the two primary outcomes in the PETHEMA trial as complete response, near complete response and partial response (CR+nCR+PR) and CR/nCR. However, these appear have been reported as complete response in the corresponding journal publication for the PETHEMA trial. Please could you clarify this?

A6. **Priority question.** With regard to the IFM trial, it is stated on page 54 (section 6.3.2.2) that '*.... the results of the VD and VAD arms with DCEP are not reported*'. On page 82 it is stated that *'stratified results based upon patient receipt of DCEP are not reported.*' However, results from the IFM trial (reported in relevant tables 24 – 53) have different n values (VAD n=121 or 242; VD n=121 or 240). Please clarify and submit the correct data.

A7. In Section 6.3.4 and table 18 (page 63-64), baseline characteristics were reported to be 'well balanced between treatment groups'.Please confirm if any statistical tests performed to support this? If so, please provide the results, for example the p-values, to support this.

A8. In section 6.3.6, page 68, the 'safety analysis set' is defined but no definition for the ITT population has been provided – please define.

A9. In figure 11, page 76, the PETHEMA flow diagram reports 386 patients as randomised whilst the journal publication reports 390 patients were randomised but 4 were ineligible. Please explain the discrepancy in terms of the ITT population.

A10. **Priority question.** Overall response rate (ORR) is defined as CR+nCR+VGPR+PR (page 67). However, in table 24 (page 83), for the PETHEMA and GIMEMA trials particularly, the data presented for ORR does not correspond to the sum of the data for the response rates individually. Please explain.

A11. **Priority question.** The GIMEMA trial publication reports 'VGPR *or better'* and 'PR *or better'* – how do these differ from VGPR and PR (values feeding into the ORR) reported in table 24 on page 83?

A12. **Priority question.** Please clarify how the response rates in table 24 (page 83) of the submission correspond with the response rates in the PETHEMA trial publication. For example, table 24 of the submission gives a percentage achieving PR of 35.4% on VTD, which compares with a figure of 25% for PR on VTD given in table 2 of the journal publication.

A13. Please clarify why some data points relating to progression-free survival are reported as "not reached" in table 25 on page 85 of the submission.

Section B: Clarification on cost-effectiveness data

B1. **Priority question.** Please explain the approach and rationale taken in the economic model with respect to maintenance therapy during the post stem cell transplant (STC) period.

B2. **Priority question.** Please clarify if the figures in table 50 on page 123 of the submission relate to the PETHEMA or GIMEMA trial.

B3. **Priority question.** The caption for table 52 in the submission is 'Total SCT rates' but it has been noted that this was amended from 'SCT rates by post-induction response category' in an earlier version of the submission. If this data (i.e. breakdown by response category) is available please consider submitting it.

B4. In figure 14, page 85, please confirm that the graph marked (A) corresponds to the Hovon trial; that marked (B) corresponds to the IFM trial; that marked (C) corresponds to the PETHEMA trial and that marked (D) corresponds to the GIMEMA trial.