NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Single technology appraisal (STA) of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171) [ID667]

Dear [redacted],

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th November by Celgene. 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 **5pm** on 12th December. 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 Carl Prescott, Technical Lead (carl.prescott@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George

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Associate Director – Appraisals
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Encl. checklist for in confidence information

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Section A: Decision Problem

A1. On page 13 of the submission it is stated that no additional evidence is likely to be available in the next 12 months. Could you please confirm that this is still the case?

A2. On page 16 section 1.13, it is explained that a safety warning regarding an increased risk of AML progression for patients with MDS was issued on 10th June to health care professionals. Please provide detail about what the safety letter describes regarding the increased risk of AML progression for people with multiple myeloma.

Section B: Clarification on clinical-effectiveness data

B1. **Priority question**: The search strategy limits searches by themes such as 'relapse' and 'recurrence' (page 216, lines 6-12 of the MEDLINE strategy), which could affect the retrieval of potentially relevant studies (e.g. Bendamustine studies). Therefore:

- Please provide the rationale for this decision.
- Please re-run the effectiveness searches removing this cluster and list any additional studies not previously identified.

B2. **Priority question**: All adverse event data provided is from the MM-010 and MM-009 clinical trials. Given the adverse event profile associated with lenalidomide, please provide the rationale for not conducting separate searches for adverse events.

B3. **Priority question**: Please provide the number at risk for figure 11 (as presented for figure 10)

B4. **Priority question:** There are values in Table 19 (page 76) which appear counterintuitive (for example baseline plasma cell percentage and duration of MM). Please confirm whether the values in Table 19 are correct and provide the equations used in the Cox regression model.

Section B: Clarification on cost-effectiveness data

B5. **Priority question**: Given the sensitivity of the cost-effectiveness estimates to the data sources in TA171, please explore the impact of using different data sources for the effectiveness data on the final ICER. More specifically, please conduct sensitivity analysis using MM-009 data only and pooled data (from MM-009 and MM-0010).

B6. **Priority question**: On page 136 of the submission there is reference to the multivariate equations developed to model OS, PFS and TTF. These equations are said to be used to adjust for differences in baseline characteristics of the populations (page 136, page 138 and page 148). Please provide these equations in full detail. Please provide the calculations performed to “improve exchangeability…and to adjust median survival estimates for lenalidomide” (page 148).

B7. **Priority question**: Pages 139 to 146 describe six parametric distributions for each clinical outcome (PFS, TTF and OS). The observed KM survival plots and parametric

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curves are provided. For the 3 outcomes PFS, TTF and OS, please provide the raw data used to produce:

- 1) the KM curves
- 2) the parametric curves
- 3) the log cumulative hazard plots

B8. **Priority question**: Please clarify which of the following approaches were taken in the economic analysis:

- The dataset was stratified and so only data (clinical and cost) for the second-line treatment population was included in the economic analysis.
- Data (clinical and cost) from the full MM-010 population was used (as suggested in page 137 - 139), and then the covariate estimate for the second-line setting was used to adjust the models results
    a. If this approach was used please present sensitivity analysis using only data from patients treated in the second-line setting

B9. **Priority question**: The Gamma distribution visually seems to be as good (or better) a fit to the KM data for PFS and TTF than the lognormal distribution, which was included in sensitivity analyses. Please clarify why the Gamma distribution was not considered in the sensitivity analysis.

B10. **Priority question**: Please clarify why the Markov trace figures for OS provided in the appendix appear to be substantially different from Figure 28 in the submission, presenting the predicted survival?

B11. **Priority question**: Please outline why no search terms for health related quality of life were included in the searches?

B12. The ICERs in this submission differ significantly from those presented in TA171. It will be beneficial to the Appraisal Committee to understand the reasons for this. Therefore please provide reasoning for this difference.

B13. Please confirm that in Table 41 the intercept term coefficient value is 3.116 and the Beta-2 microglubin coefficient -0.779 for the log-logistic model (The same applies for the lognormal model coefficients).Please provide the p-values used to assess the statistical significance of the predictors.

<u>Textual clarifications and additional points</u>

1. **Priority question**: Please consider the following and provide an updated model if necessary:
    - The values on tab “Comparative efficacy” could not be traced back in the submission. The values for median OS and median PFS for the Len/Dex arm of the model do not match the values provided in Section 6 of the submission. Please present these outcomes and the sources.

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- Within the same excel tab, there is potential mislabelling in the tables from cells C32-J78. Please provide a clear, corrected table with sources included.

2. **Priority question**: The Excel model provided indicates that there are extra calculations to adjust for the crossing of the fitted PFS and OS curves, which may have led to an overestimation of PFS. Please provide the rationale for these calculations.

3. **Priority question**: In the Excel model provided, there is a possible inconsistency in the approaches to adjust for patient characteristics. The median observed PFS and TTP (tab “Comparative Efficacy”, cells F44 and F45) are not adjusted for patients characteristics reported in the Taverna study, whilst the median OS estimate was. Please provide median PFS and TTP from trial MM-010, adjusted for patient characteristics from the Taverna study.