Celgene
United Kingdom

17th June 2014

National Institute of Health and Care Excellence

1st Floor, 10 Spring Gardens
London – SW1A 2BU

Dear Jeremy,

Re: ERG additional critique - multiple myeloma - lenalidomide (part rev TA171) [ID667]

Following our correspondence yesterday, set out below is a brief description of the key factual inaccuracies in the ERG critique, for the Committee and the ERG to consider. I hope this will assist discussion at tomorrow's meeting.

1. Celgene has identified a key error in relation to the method that the ERG has applied to re-estimate the ICER for lenalidomide vs. bortezomib retreatment (page 59). The ERG has miscalculated the bortezomib PAS, applying a discount of 85% where the PAS is taken up (rather than 15%) and in doing so vastly underestimating its cost. Correcting their formula makes the ERG ICER equivalent to the PAS calculation used by Celgene. This therefore invalidates all of ERG's ICER's and their conclusions regarding the cost-effectiveness of lenalidomide.

2. We note that throughout the ERG report, the tone and the direction of the critique to the Celgene response and particularly the efficacy modelling (i.e. curves crossing, see ERG critique pages 27, 33, 37) appear to imply that Celgene had not considered the issues raised previously. This is factually incorrect. It should be noted that all re-analyses provided by Celgene in response to the ACD were fully confirmed and agreed with NICE as per email correspondence dated 20th March 2014 and copied here – *".. In the ACD we state that obtaining the best fit for a curve and the natural history of disease, rather than preventing curves from crossing, should form the basis for selecting a curve. The Committee is content with the piecewise exponential curve to be used because of the more plausible long term survival..."*

3. In a number of instances the ERG state or suggest that a particular analysis was not conducted by Celgene:

(i) Bortezomib PAS (page 57), however this was included in the revised analysis base case results (see Celgene ACD response page 37)
(ii) Analysis with bortezomib treatment duration of 8 cycles (page 60), however this was included in a scenario analysis (see Celgene ACD response page 47)
(iii) Utility scenario analyses (page 75), however Celgene do not only consider utility associated with disease progression as suggested (see Celgene ACD response page 35).
(iv) Information on age not provided in utility from Palumbo paper (page 63), however this information is publicly available from the MM-003 trial population.
(v) Raw data used to produce survival curves (page 29), however this was provided in response to the ERG request for clarifications.
(vi) Covariates included in the regression models for clinical outcomes (page 29), however these are available in Table 14.2.5.1A in the MM-009 and MM-010 CSRs.

4. Furthermore, the ERG notes that the stepwise regression equations were requested in full (page 30), however this request was never received and we therefore queried this with the Institute in an email dated 13th June.

5. The ERG questions allowing bortezomib treatment for longer than 8 cycles, citing that only 2% of patients in the Taverna *et al* study were treated for 10 cycles or more. This disregards the clinical expert in attendance at the last Appraisal Committee meeting who advised that this is varied in UK practice. Furthermore, the Taverna *et al* study did not provide Kaplan-Meier curves with which we could reasonably estimate treatment discontinuation.

6. The ERG question the value of including third and fourth-line treatments (page 55). However, scenario analyses were presented to explore this, including entirely omitting these treatments and including them identically for both model arms. These analyses show lenalidomide to remain highly cost-effective, for example, when subsequent therapies are omitted the ICER is £3,893 (see Celgene ACD response page 46).

I do hope that this is helpful and I look forward to the discussion tomorrow.

Best Wishes

Sujith Dhanasiri

Celgene Ltd, UK & Ireland.