19th February 2009

Dr Carole Longson,
Director, Centre for Health Technology Evaluation,
National Institute for Health and Clinical Excellence,
MidCity Place,
71 High Holborn,
London,
WC1V 6NA

Dear Dr Longson,

Lenalidomide for multiple myeloma in people who have received at least one prior therapy – Celgene comments on the appraisal consultation document

As invited in the email dated 23rd January 2009, we are pleased to offer these comments on the above appraisal consultation document (ACD). As requested, our comments will be organised under the four general headings.

Thank you for the opportunity to respond to the ACD. Herewith are our remarks.

i) **Do you consider that all of the relevant evidence has been taken into account?**

We believe that the appraisal considered all of the relevant evidence for the use of lenalidomide in previously treated multiple myeloma that was available. Celgene would like to endorse the Committee's decision that the appraisal of lenalidomide fulfilled the criteria for supplementary advice as a life-extending therapy. We wish to provide further clarity to the Committee's decision given that Celgene was unable to comment on the 'end of life criteria' in our response to the first ACD in October 2008. The criteria and our supporting evidence are set out below:

1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months;

From a historical perspective, overall survival in patients receiving one prior therapy for multiple myeloma has been estimated at a median of 14.4 months

(1.2 years) from a retrospective analysis of UK Myeloma trials IV, V, VI and VII between 1980 and 1997 (n = 2,528) [1].

Thus, overall survival in patients who have received at least one prior treatment is very likely shorter than 24 months. The findings in the control arm of the MM-009/010 trials are confounded due to the permitted cross-over from dexamethasone to lenalidomide. The observed overall survival for patients treated with dexamethasone reached 31 months (NICE submission pages 84-85), but 47% of patients had crossed over to lenalidomide following disease progression or study unblinding.

Further analyses of these Medical Research Council (MRC) data revealed that median overall survival for patients with one prior therapy was 16.1 months and for at least two prior therapies was 9.2 months (NICE submission pages 114-115 and Appendix 8). Even when adjusting these MRC overall survival data for the characteristics of patients treated with dexamethasone from MM-009/010 the survival remained well below 24 months for both one prior therapy (19.5 months) and at least two prior therapies (11.6 months) (NICE submission pages 114-115 and Appendix 8).

Given the position of lenalidomide and dexamethasone following at least two prior therapies, it is without doubt that the expected survival (life expectancy) is less than 24 months with current standard treatment.

2. There is sufficient evidence that the treatment offers an extension to life, normally of at least an addition 3 months, compared to current NHS treatment;

The pivotal MM-009/010 studies demonstrated that the median overall survival in patients who have received at least one prior therapy was improved by more than 3 months (lenalidomide/dexamethasone vs. dexamethasone) even without adjusting for the cross-over to treatment with lenalidomide following disease progression or study unblinding.

In the updated MM-009/010 data cut in January 2007 the median overall survival with lenalidomide/dexamethasone was 35 months (149.7 weeks) compared with 31 months (133.3 weeks) in the dexamethasone arm (NICE submission pages 84-85).

Further analysis of the MM-009/010 overall survival data by number of prior therapies demonstrates that the extension of life remained substantially in excess of 3 months regardless of number of prior therapies. For patients with one prior therapy the median overall survival with lenalidomide/dexamethasone was 39 months (169.1 weeks) compared with 33.5 months (145.4 weeks) in the dexamethasone arm (NICE submission pages 87). For patients with at least two prior therapies the median overall survival with lenalidomide/dexamethasone was

33 months (144.0 weeks) compared with 27 months (118.0 weeks) in the dexamethasone arm (NICE submission pages 87).

Importantly, following adjustment for the cross-over effect the extended survival was 19.5 months (39 months – 19.5 months) in patients who had received one prior therapy and 21.4 months (33 months – 11.6 months) in patients who had received at least two prior therapies (NICE submission page 87 and pages 114-115).

Celgene believes that this evidence categorically demonstrates that Revlimid meets the criteria for extending life.

3. No alternative treatment with comparable benefits is available through NHS;

Celgene would like to endorse the Committee's decision that there are no alternative treatments with comparable benefits available through the NHS.

Bortezomib (Velcade) is currently recommended by NICE for patients who have received one prior therapy only and by definition is not widely available through the NHS for patients who have received at least two prior therapies as it was deemed unlikely to be cost-effective in the completed technology appraisal (TA129).

Thalidomide, as per the Committee's decision comments, is only licensed as a first line treatment and is not licensed in previously treated multiple myeloma. Furthermore, there is no evidence to support the effectiveness (or comparable benefit) of thalidomide in patients who have been treated with two or more prior therapies.

Dexamethasone or other conventional therapies are available through the NHS, but they do not have proven comparable benefits to lenalidomide. Indeed, dexamethasone was proven in studies MM-009/010 to be inferior to lenalidomide/dexamethasone.

Thus, Celgene believes that no alternative treatments are available through the NHS with comparable benefits to lenalidomide.

4. The treatment is licensed, or otherwise indicated, for small patient populations.

Lenalidomide has been granted orphan status by the Committee for Orphan Medicinal Products, on the basis that multiple myeloma is not only rare (occurring in fewer than 5 in 10,000 persons in the European Union), but is both life threatening and debilitating, in addition to representing a disease with significant unmet medical need. Treatment of multiple myeloma with lenalidomide was

entered in the Community Register of Orphan Medicinal Products under the number EU/3/03/177 on 12 December 2003.

We estimated the number of patients in the UK who have had 2 prior therapies and therefore are eligible for lenalidomide is approximately 2,100.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We agree that the summaries in the ACD are reasonable interpretations of our submissions and the ERG analyses. However, we maintain that the use of median in the survival analysis is a correct analysis based on our scientific reasoning in previous communications. We are pleased that the Committee noted in Section 4.15 that the 'choice between using mean or median survival was a scientific judgment' and, although calibration to the mean was determined to be the reviewer's preferred approach in this case, we respectfully withdraw from further discussions on this methodology.

We agree that, using the ERG approach and the second analysis we submitted, the ICERS are £43,800 (1.81 life years gained and 1.24 QALYs gained) for two or more prior therapies and £41,300 (1.71 life years gained and 1.15 QALYs gained) for prior therapies including thalidomide (Section 3.22).

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

We agree with the Committee's recommendations based upon the submitted data, the nature of multiple myeloma and the value placed on the benefits of lenalidomide by patients, their carers and clinical experts.

We strongly concur with the Committee's consideration that the extended life years in this patient population might be given full quality weight in determining the ICER. The Committee commented that 'the magnitude of the additional weight that would need to be assigned to the original QALY benefit for the cost effectiveness of lenalidomide to fall within the currently applied ICER threshold range was acceptable.' We are pleased that the Committee has made this consideration for the option to use lenalidomide for the treatment of multiple myeloma patients who have received two or more prior therapies. The *quantitative exploration* provided by the review team adopts the van Agthoven et al.[2] estimation of a health utility value of 0.81 for the multiple myeloma patients alive and 'healthy' for this population and we concur with this approach as having a basis in the published literature.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

We do not know of any equality related issues not addressed in the ACD.

References
1. Drayson MT, Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, et al. Survival from relapse and the influence of therapy. Haematologica/The Hematology Journal: XIth International Myeloma Workshop Proceedings 2007;92(6, s2):173-, Abstract # PO-665.

2. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der HB, Lokhorst HM, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. Eur J Cancer 2004 May;40(8):1159-69.

We have no further comments on the evaluation report.

Yours sincerely,

[redacted]

Celgene Ltd
Morgan House
Madeira Walk
Windsor
SL4 1EP