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Dear [redacted]

Re: Single Technology Appraisal – Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

The Evidence Review Group (Kleijnen Systematic Reviews) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 8 January 2013 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 **10am, Friday 15 February 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 [redacted] – Technical Lead ([redacted]). Any procedural questions should be addressed to [redacted] – Project Manager ([redacted]) in the first instance.

Yours sincerely

[redacted]
[redacted] – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: General requests: Clarification on search strategies

General

A1. In order to reproduce the searches, please confirm the following details for all database searches for sections 10.2, 10.10 & 10.12:

- Although the manufacturer submission (MS) states that no date limits have been applied, please provide the date span searched for each search and each individual database i.e. Medline 1946-2013/01/22
- Although the MS states in each section the date of the week commencing for each set of searches, please provide the exact date each individual resource was searched on.

Clinical Effectiveness Searches (6.1 &10.2)

A2. Please confirm if the Medline strategy reported in 10.2 also included the search of Medline In-Process (as requested by NICE). If not, please confirm if this was searched and provide the relevant strategy.

A3. In section 6.1 the MS states that the Web of Knowledge Conference Proceedings Index was searched, but there is no record of this in section 10.2. Was this included in the Science Citation Index Search? If not, please confirm if this was the case and provide a strategy.

Adverse Events Searches (6.9 & 10.8)

A4. **Priority request:** Please clarify whether any Adverse Events searches were undertaken? If they were carried out, please provide the full details of all searches, including the date spans, date searched and strategies used. If Adverse Events searches were not carried out, please provide further explanation for not completing these.

Cost Effectiveness Searches (7.1 & 10.10)

A5. Econlit is included in a list of databases searched in section 6.1, but there is no record of this in section 10.10 or elsewhere. Please confirm if this was searched for in the Economics section as requested by NICE. If it was, please provide the search strategy.

A6. Please confirm if the Economics Medline strategy reported in 10.10 also included the search of Medline In-Process. If not, please confirm if this was searched and provide the search strategy.

Measurement of Health Effects HRQL Searches (7.4 & 10.12)

A7. Section 10.12 includes a single generic search strategy; please clarify whether the individual search strategies for this section are those recorded in 10.10 as "Utility Values Strategies".

A8. Please confirm if the Utilities Medline strategy reported in section 10.10 also included the search of Medline in Process, if not please confirm if this was searched and provide the search strategy.

A9. Please confirm if the search strategy for NHS EED reported for the Economics search in 10.10 was also used to inform the HRQL section (10.12).

A10. Econlit is in the list of databases searched in section 6.1, but there is no record of this in section 10.12 or 10.10. Please confirm if this was searched in the HRQL section as requested by NICE. If it was searched, please provide the search strategy.

A11. In section 10.12.1 the MS states that Web of Knowledge Conference Proceedings Index was searched, please clarify if this was included in the Science Citation Index Search? If not, please provide the search strategy.

<u>Section B: Clarification on the clinical effectiveness data:</u>

B1. **Priority request:** Please provide the complete clinical study report (CSR) for the MDS-004 study, including information such as the demographic and baseline characteristics of the ITT population (Table 14.1.3.2).

B2. Please provide a list of excluded studies by reason of exclusion, in particular the 18 studies excluded because of "intervention not of interest" and the 17 studies excluded because of "outcome not of interest".

B3. Please clarify how the additional publications in table 4 (page 38 of the MS) were identified, and whether there is a reason why were these not identified through the systematic search (for example, studies 3, 8, 9 and 10 seem to fulfil all inclusion criteria)?

B4. In the study population flowchart (Figure 4, page 45), please provide the reasons for exclusion from the mITT analysis by treatment arm.

B5. **Priority request:** Please clarify the main 'other' reasons for discontinuation for both the lenalidomide groups with the corresponding numbers (see table 8, page 55 of the MS).

B6. **Priority request:** Page 56 of the MS states "that the deaths only reflect those whose discontinuation page listed death as the reason for discontinuation

from the study, and do not reflect the total number of deaths reported." Please clarify the actual number of deaths by treatment group and study period.

B7. **Priority request:** Please provide all results reported in chapter 6.5 both for the ITT and the mITT population; including: Time to erythroid response; Duration of erythroid response; Change in haemoglobin levels; Cytogenetic response and progression; HRQoL; Disease progression and Survival. Currently, the MS only includes Erythroid response reported fully, other outcomes are only reported for the ITT population (Time to AML progression) or for the mITT population (Duration of erythroid response).

B8. The scope states: "If evidence allows, subgroups based on different cytogenetic profiles will be considered separately". Please clarify why this subgroup has not been explored in the MS (see MS, statement of the decision problem, page 28)

B9. Please clarify the following sentence on page 30 of the MS: "Add in the response rates used in the HE model – assessed at day 80".

B10. In section 6.3.1 of the MS it is difficult to relate study references to each of the clinical trials. Please provide all the relevant references for each of the Celgene trials (MDS-001 to MDS-004).

B11. Page 44 of the MS states that "... patients not tolerating dose level −3 discontinued treatment", please clarify which treatment options were available for these patients? BSC only or also other treatments such as azacitadine?

B12. **Priority request:** Please clarify why a relatively large number of patients were excluded from the mITT population (66 out of 205), and the reasons why most of these did not fulfil the inclusion criteria (n=20) or had inadequate/insufficient information (n=44). Please clarify why it was not possible to assess people fully before randomisation?

B13. Please provide full definitions of Erythroid response according to the IWG 2000 and 2006 criteria.

B14. **Priority request:** Please provide an overview of patients that crossed over from one arm to another with time of cross-over and from which arm to which arm and how these treatment switches were handled in the analyses.

B15. Please provide possible reasons why AML progression in the MDS-004 trial is so much higher compared with untreated del(5q) MDS patients in other publications (see ref 84-Germing 2012).

B16. Please provide a description of the FACT-An scale and provide references.

B17. In table 14 (page 80) of the MS, please confirm that the last column is 10mg, instead of the 5mg reported.

B18. Figure 7, page 65 of the MS presents subgroup analysis of erythroid response (lenalidomide 10mg vs 5mg). Please provide the same figure for both lenalidomide arms separately versus placebo (preferable for the ITT population, or both mITT and ITT).

B19. On page 45 of the MS it is stated that: "Patients with disease progression at any time and those randomly assigned to lenalidomide 10 mg without minor erythroid response by Week 16 were withdrawn from the study and were ineligible for open label treatment." Please clarify how data for these patients were analysed in the mITT analyses – were they still followed-up for outcomes, were their results censored, what happened if they died?

B20. **Priority request:** Please provide tables with adverse events as reported in chapter 6.9 for the per-protocol population.

B21. **Priority request:** Please clarify the diagnostic process for the ITT population and the mITT population and clarify how the tests used and diagnostic process of determining IPSS risk, del5q31 status and transfusion dependence in the clinical studies compares with standard NHS practice?

B22. **Priority request:** In the MDS-004 trial, please explain which patients in the control arm received placebo only or placebo plus best supportive care (BSC). Please clarify what constitutes BSC in the MDS-004 trial. For instance, how many patients received erythropoiesis stimulating agent (ESA), GCSF, or blood transfusions as part of BSC; and what other treatments were allowed as part of BSC?

Section C: Clarification on the cost effectiveness data:

C1. Please specify the parts of the submission with clinical expert input. If clinical experts were consulted, please provide the rationales for your decisions on validation of the model structure and the main model assumptions.

C2. Please describe the search process for identifying literature on transition probabilities (e.g. probability of diabetes or cardiac disease) and costs (e.g. costs of diabetes and other complications) that were not based on the lenalidomide clinical studies. Please elaborate on the studies identified and their applicability to this study population.

C3. Page 97 of the MS describes the model structure. Please explain how patients with existing rather than acquired cardiac conditions and diabetes are accounted for? Is the treatment/outcome profile different for these patients?

C4. Page 97 of the MS describes the model structure. Please explain why progression to more severe forms of MDS was not included within the model?

C5. Page 101 of the MS states that 28% of UK patients in the trial had received ESA prior to the trial but that 52.7% of all patients in the trial had received

ESA prior to the trial. Please clarify the rationale for the assumption that the proportion of patients who received ESA prior to the trial is representative for ESA use during BSC in the UK.

C6. **Priority request:** Page 102 of the MS describes the assessment of response. Please clarify why a 84-day assessment period was used for determination of response rate in the HE model, while in Ch. 6 of the MS only a 56-day and 182-day assessment period were reported (as per protocol).

Also, please explain the impact on model outcomes of using a smaller or larger number of days for the assessment period

C.7 Please provide further explanation of 'major response' as mentioned on page 102 in the MS, indicating whether a minor response may also be obtained. Please provide definitions of major and minor response where appropriate.

C8. **Priority request:** In the last paragraph on page 102 of the MS numbers are presented about treatment interruptions. None of the numbers cited in this paragraph match the numbers used in the model [excel sheet Dosing]. Please explain the discrepancy.

C9. **Priority request:** Page 103 of the MS states that treatment interruptions were experienced by 64% of the ITT patients that are on treatment. Please clarify if this 64% is based on 10 mg lenalidomide, 5 mg lenalidomide or both? Please provide the percentage of treatment interruptions per treatment arm.

Further, 62% of the patients experiencing a first interruption also experienced a second interruption. After the second interruption patients resumed treatment at a dose of 5 mg for 14 days per cycle. Please provide sub-analyses from the trial about their response and overall survival.

Experience from the Cancer Drugs Fund indicates a 23% probability that patients will switch to a lower dose. This 23% appears low considering the 64% chance of treatment interruptions followed by treatment adjustments in the trial. Please clarify this apparent discrepancy.

C10. Page 106-107 of the MS states there was no reported ESA usage during the trial, therefore available literature was used to estimate response rates in these patients. While the response rate for ESA+G-CSF was calculated as 21.7%, this was reduced to 10.8% for ESA and G-CSF monotherapy. The published response rates to ESA range froms 10-49% for ESA compared to around 50.6% with G-CSF, so the current estimate of 10.8% appears low, please clarify the choice of estimate?

C11. On page 108 the MS states that the results show that the order patients received treatment (and therefore crossover) did not have a significant impact on duration of response. Please provide these results. Please clarify whether patient numbers are sufficient to detect significant differences?

C12. Please provide further rationale for why the 5mg dose efficiency was used as a proxy to determine the response curves for the best supportive care arm in the model (page 108 of the MS). Please clarify the process taken to identify the value used for BSC and to determine its appropriateness, for example searches for contextual data available in the literature.

The excel sheet (Response KM), the KM curve shows (although based on only a few patients) a better response for placebo in the first 5 cycles than for 5mg and it actually appears closer to the 10 mg curve. In light of this, please justify why the 5mg group may be used as a proxy for BSC.

C13. Page 109 (figure 13) of the MS shows the KM curve for responders in the lenalidomide 10 mg and 5 mg treatment arms. Please explain why there are 75 patients at risk if there were 69 in the ITT 10 mg group? Also, the KM curve of the 10 mg group seems similar to the 5 mg except for the plateau at the start. Do you have any explanation for this plateau?

In addition, the excel sheet (Response KM) in the model looks very different from figure 13. Also, the patient numbers presented on that sheet do not match those in the trial arms. Please explain this discrepancy.

C14. Please clarify the rationale (page 113 of the MS) for assuming that there are no differences in blood transfusion rate between cardiac, diabetes, hepatic conditions as well as AML?

Please also clarify the rationale for assuming that there are no differences in blood transfusions/platelets per cycle rate between cardiac, diabetes, HC as well as AML and also with disease progression?

C15. Page 114 of the MS details previous transfusion history. The MS states that patients who have had a total number of units greater than the threshold at which iron chelation is applied are excluded from this analysis as they are assumed to start the model in the iron chelation health state (8% of the UK patients). Please provide the treatment allocation of these patients.

C16. **Priority request:** Page 115 of the MS states that two different treatment choices for iron chelation are considered, based on the Prescription Cost Analysis: England 2010. However, that database also lists deferiprone as a prescribed treatment option. Please clarify why this drug was not considered in the model. Please also explain how the 71% for the Exjade was derived from the database, as the ERG obtain 74% based on Pxs and 80% based on Qty.

C17. Please provide justification for the assumption of response to iron chelation in the first cycle (page 115 of the MS). Also please explain how different assumptions of time of response would impact the model outcomes.

C18. In the last paragraph of page 120 of the MS a description is given about the use of a GAM model to fit the ACM data. Please provide more details about this model. Also please explain how this relates to the curves in figure 21 of the MS, and how it relates to the calculations in the excel model.

C19. **Priority request:** Page 124 of the MS indicates that only two adverse events were included in the model. Please explain why only these two were included and why others, for example DVT/PE were not included?

C20. Please justify why adverse effects of lenalidomide only occur in the first 4 cycles (page 125 of the MS).

C21. Please explain how from ref 86 the numbers for complications of iron overload in table 27 of the MS (page 125) were derived.

C22. Please provide further explanation of the generalizability of the results of Malcovati et al. (ref 76) to the current model (page 126 of the MS), especially regarding the population and the definition of transfusion dependency. Also please clarify how uncertainty around the estimated curve was estimated, since no patient-level data was available.

C23. Utility values were obtained from Szende 2009 ref 99 (page 148 of the MS). The model is highly sensitive for the utility values per health state. Please explain if other options for utility estimation have been explored, such as the use of the CALGN 9221 study, in which EORTC score were collected which can be mapped to EQ-5D.

C24. Please provide further justification for why the utility estimate for AML was assumed to be the same as for patients who were transfusion dependent (page 148 of the MS).

C25. Please explain which tables and numbers where used from the Fryback (1993) publication to derive the AE utility decrement for cardiac disease and diabetes applied in the model (page 149 of the MS) and whether a systematic search was undertaken to obtain more contemporary estimates.

C26. Please provide further justification for why no utility decrements were applied to the lenalidomide related SAE (i.e. neutropenia and thrombocytopenia). The effects are argued to be “typically transient and manageable and QoL is likely to be short term” (page 149 of the MS). However no evidence is provided for this. Can it be provided?

C27. It is currently assumed in the economic model that all monitoring of MDS is completed by a GP (page 156 of the MS). Please clarify how this assumption was derived and its justification.

C28. Please provide further justification for the assumption that all patients are assumed to have the same monitoring frequency (page 156 of the MS).

Specifically comment on the assumption that non responders require the same amount of monitoring as responders.

C29. Please explain why fixed cost estimates were used for chelation (page 156 of the MS), despite the fact that treatment is weight related, leading to variation in costs between patients?

C30. Please provide the document from which the UK costs of AML were retrieved and indicate on which page the cost estimate of £1,844 per 28 day cycle can be found (page 158 of the MS). The ERG were only able to find an estimate of £1,814 per 5-week cycle (page 100 of the MS for the STA of azacitidine). Please also clarify if any treatment costs for AML such as chemotherapy or stem cell transplantation are included in this cost estimate.

C31 **Priority request:** Please explain why reference costs for SA08F (page 160 of the MS) were used even though there are specific codes for thrombocytopenia (SA12D with cc and SA12F w/o cc) and for febrile neutropenia (PA45Z)?

C32. Please justify why the number of monitoring visits for BSC and lenalidomide is not varied in the PSA (page 163 of the MS).

C33. Please justify the use of a standard error of 10% of the mean for various parameters in the sensitivity analyses (page 162 of the MS). Please clarify why 10% was used rather than for example 20%? Also whether there was any data available that could inform the uncertainty around the mean estimates?

C34. **Priority request:** At section 7.7 (page 172 of the MS), in the response to question 7.7.1, no information is provided about the methods used to validate the model internally and externally and how technical validity was assured.

Regarding the internal validity, some information is already provided in table 40, however, no discussion is provided on the degree of concurrence between trial results and model results, for example, the differences in the median overall survival for lenalidomide between the model and trial. Besides medians, please also provide restricted means as a measure to compare the trial with the model outcomes.

Regarding the external validity, please compare the model results to data sources outside the clinical trial. This is especially relevant for the BSC group.

C35. The proportion of patients achieving transfusion independence in the 10mg lenalidomide arm is similar between the mITT (61%) and ITT (60.9) (page 175 of the MS). Please provide a similar comparison for the other treatment arms (i.e. 5mg and placebo). Also please indicate how similar results are for overall survival in the different treatment arms.

C36. Section 7.9.1 (page 176 of the MS) asks about consistency of results to other economic analyses – the answer relates to analysis of sub groups. Please provide a response to this question about the extent to which the current HE outcomes are consistent with published economic literature.

Issues regarding electronic model:

C37. Excel model sheet Transfusion: Please explain the variable "Increase in transfusion rates per cycle" 1%

C38. Excel model sheet Sensitivity Analysis: Please explain why for the lower and upper bound of the parameters a 90% confidence interval was used rather than the 95% interval. For example for the response rate lenalidomide:

- Sensitivity Analysis sheet upper and lower bound 0.597 – 0.621;
- Response sheet CI 0.484 – 0.724

C39. **Priority request**: Please clarify how the uncertainty around the risk of cardiac disease in chelation was modelled. Table 28 indicates a multivariate normal distribution for the parameters of the Gompertz curve. However, on the sheets Parameters and PSA-parameters, these variables seem fixed.

C40. Please explain the role of the KM curves on the excel sheets Response KM, DeathnoAML KM and AML KM. Please indicate where are they used in the model calculations.

C41. **Priority request:** Excel model sheet Response: Here it states: "We assume that response to treatment occurs within the 1st 4 week cycle, so all patients spend the 1st cycle in the transfusion dependent state." However, on work sheet PF_revlimid this does not seem to be the case, in the first cycle already 60% of patients are in the transfusion independence health state. Please clarify the assumption made.

C42. **Priority request** Excel model sheet PF_SC: In column Y of this sheet the probability of response to GCSF is estimated multiplying p_percentESA (28%) and p_RespTIGCSF (2.4%). However, p_RespTIGCSF is defined on sheet Response as prop_ESA (28%) * m_RespTIEsa (8.4%). Thus, it appears that a correction for percentage of patients receiving ESA has been made twice by accident. Please explain whether this is indeed a programming error or if not, what the rationale is for weighting the response rate of GCSF twice.

C43. **Priority request:** Table 23 on page 106 of the MS shows the response rate for the ITT population. The mean is 7.5% for the placebo group. To get the overall BSC response rate, this trial response rate is weighted with the ESA response rate (10.8%) in order to derive an overall BSC response rate of 8.4% [excel sheet Response cell I50]. However, in [excel sheet PF-SC G23] again a weighted average is calculated, this time of the 8.4% that was previously derived and the 7.5% of the placebo group. It appears that the

weighting has been applied twice. Please explain whether this is a programming error or if not, the rationale for weighting the response rate twice.

C44. Please explain why the dosage interruptions were modelled using a simple mean time to interruption that is applied to the whole cohort. Please justify why the patient level data on dosage interruption was not used to estimate a percentage interruption for cycle 1, 2, etc.to mimic reality better, where some patients have an interruption after 1 cycle and some after several cycles.