National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenic abnormality in people with red blood cell transfusion dependence

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Kleijnen Systematic Reviews Ltd* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by ***5pm, Tuesday 19 March*** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29 October 2009

Major Issues

Issue 1 Missing ERG conclusion on ITT / mITT populations from the summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12 ITT and mITT in point 2	We request that point 2 be amended to include the following statement based upon later ERG conclusions "however as the number of patients who do not match the expected license indication is small and reasonably balanced, the trial sufficiently represents the target population."	The ERG conclude on page 68 that "Information about the ITT and mITT was requested in the clarification letter regarding the reasons for exclusion per group. Table 4.4 shows that the number of patients who do not match the expected licence indication (i.e. INT-2 or higher IPSS score and no del5q by central review) is small, four and seven patients in the placebo group and lenalidomide 10mg respectively, and reasonably balanced. Therefore, the ERG concluded the trial sufficiently represents the target population."	Not a factual error, no change made.

Issue 2 Statement that model neglects impact of ESA is not factually correct

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Page 74 "The model neglects this positive effect in the comparator group by using only the initial response rate."	We would request that this statement be removed as it is factually incorrect.	The initial response rate is increased in the model when ESA / GCSF is included as the additional expected responders above the rate for placebo are assigned the mortality and AML progression profiles for responders derived from all arms of the MDS004 trial. Note	We do not consider this a factual error. Maybe the term initial response rate raises some confusion. The probability of death is based on the response rate of transfusion independence in the first cycle including both

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		that the life year estimates differ when comparing BSC as 100% transfusion to BSC where ESA is included for this reason.	response to BSC and ESA. However, due to the addition of G-CSF, the response rate increases in the fifth cycle. While the initial response rate does indeed account for the effect of ESA, the model does not account for the effect of G-CSF on mortality. Note that in the ERG base case, this issue is corrected.

Minor Issues

Issue 3 Statement regarding unreliability of clinical data not specific

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 12, 15, 58 and 11 “The possibility of treatment switching after 16 weeks due to dose-limiting toxicities or lack of response, which means that most long term effectiveness data are unreliable”	We would request that the statement be amended to be more specific as the term ‘unreliable' is too broad ranging a comment and does not take into account the different purposes for which the data might be required.	Whilst the crossover within the trial and reductions in doses due to toxicities may in theory limit the ability to understand the effect of drug at a particular dose it does not limit the ability to assess the effectiveness of the drug in a real world scenario where dose adjustment due to toxicity is likely to happen.	Not a factual error, no change made.

Issue 4 Statement regarding inability to detect differences in survival not specific

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12 and 59 "Given the short follow-up time (16 weeks) and the subsequent possibility to cross-over from placebo to active drug, chances of detecting prolonged survival or acceleration of leukemia progression are limited"	We would request that the statement be amended to clarify that this refers to prolonged survival or acceleration of leukemia progression by treatment arm from within the available trial data.	Whilst data obtained from within controlled randomized studies provide the clearest evidence with respect to safety and efficacy of a new treatment it is not always feasible to obtain this for a number of reasons, e.g. rare disease, small patient numbers, cross-over, trial design etc. In such instances, comparisons with historical control data can be useful if conducted carefully with appropriate measures taken to minimize bias, and where it is possible to identify patients with characteristics that closely match the characteristics of patients exposed to the new treatment. The Kuendgen 2012 paper which was referenced to in the submission was a robust assessment employing multivariate Cox regression analyses and provides strong additional information. Their study results indicate that treatment with lenalidomide was associated with an OS benefit and does not increase the risk of progression to AML. In the MDS-004 trial patients who achieved a cytogenetic response	Not a factual error, no change made.

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		with lenalidomide had a lower risk of progression to AML. This observation is consistent with the established principles of cancer therapeutics where a reduction in clone size is associated with a better prognosis. In addition and as demonstrated in the manufacturer submission the trial data was sufficient to detect a significant difference in mortality by response status.	

Issue 5 Statement that errors altered the ICER substantially over plays the impact of errors

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Page 14 " a few errors regarding the electronic model were identified that altered the results substantially"	We request that the actual change to the model results are provided rather than the statement "substantially"	We suggest that a change of approximately 10% is not substantial	This is not a factual error but a matter of judgment. Table 6.1 of the ERG report shows the ICER of the manufacturer's base case as well as the ICER after confirmed programming errors and correction of errors due to dose reduction (£66,453). After correcting these errors, the increase was £9,488 (17%). While a potential increase of almost £10,000 in a sensitivity or scenario analyses might not be substantial, this was a certain increase related to programming errors only, which the ERG does consider substantial.

Issue 6 Statement suggests that effect of treatment interruptions is not included in the model, however, as ITT analysis is used this is included

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Page 14 "in reality however, treatment interruptions will most likely also	We request that clarification is provided as this is taken into account within the health economic model through the use of ITT analysis which ensures that the impact of treatment	Any impact on effects will be captured within the analysis, as ITT analysis was performed i.e. including patients who experienced	This is not a factual error. The manufacturer is correct that in the base case analysis

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impact the effects”	interruptions on outcomes is included (as per the clinical trial) within the modelled outcomes	dose reductions in the same proportions as within the clinical trial	treatment interruptions were accounted for since an ITT was conducted. However, the statement on page 14 was provided as a comment on the sensitivity analysis. While treatment interruptions were included in the sensitivity analysis of the ICER, the effect might not be explored correctly since treatment interruptions (due to the structure of the model) only impact costs, i.e. an increase in treatment interruptions decreases costs while the response rate remains similar and vice versa. The sensitivity of the ICER might be smaller if treatment interruptions in the sensitivity analysis both impact costs and response.

Issue 7 Statement regarding utilities evidence does not make clear that no good sources are available

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Page 15 “A great weakness of the current study is the lack of high quality utility data. Given the sensitivity of the ICER to these estimates, this	We would request that this statement is clarified to point out that no alternative high quality utility data is available which could have been used in the model.	We acknowledge the lack of high quality of available utility evidence, however, all available evidence indicates similar gains in utility when patients become transfusion independent and all available	This is not a factual error. While there was indeed no high quality data available, the ERG would like to note that the manufacturer had the

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means that there is uncertainty about the correct estimate of the ICER"		evidence has been used within the model as base case or scenario analyses.	opportunity to collect utility data in order to remedy this, for example during the MDS-004 trial. However, this option was not utilized. Besides, the ERG does not consider not all evidence indicative of a similar gain for transfusion independence.

Issue 8 Incidence of diabetes and hepatic complications

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Page 72 "Given the incidence of diabetes (N=5) and hepatic complications (N=11), the total patients number (N=46) and the information on follow-up the ERG could not replicate the numbers provided in the MS and remains in doubt how these numbers were derived."	None required – info provided to ERG to clarify.	We would like to clarify (as we misunderstood the previous ERG question) that the rate was calculated using the following formula for hepatic complications. 1-(1-11/46)^(1/(38/12)) = 8.3% The diabetes rate was incorrectly calculated and should actually have been: 1-(1-5/46)^(1/(38/12)) = 3.6% Changing the diabetes rate to the above makes a difference of £13 to the ICER.	The ERG thanks the manufacturer for the clarification.

Issue 9 Discrepancy on AEs

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Page 80 “In the first case, the discrepancy between text and numbers used does not lead to problems, but if the proportion AEs is based on all grades whilst the proportion treated is based on grade 3/4 AEs, the current model is incorrect. The ERG has opted not made changes to the model.”	None required – info provided to ERG to clarify.	Both the proportion of AEs and the proportion treated are based on all grades.	The ERG thanks the manufacturer for the clarification.

Issue 10 Overestimate of impact of adverse events on utilities in sensitivity analysis – alternative suggestion for ERG consideration

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 84 "The ERG considered the reference to the study of Brown[56] who obtained the utility values from the study of Lloyd[57] which was conducted among patients with breast cancer not applicable to this patient population" A 25% utility decrement is then applied to all patients with neutropenia or thrombocytopenia as an arbitrary test of impact.	We would suggest that the proposed utility decrement of 25% be applied to treated patients only, as the numbers of patients treated (and therefore experiencing severe symptoms) are small. Doing this would produce an ICER of £62,903 – a smaller increase than the increase to £63,893 suggested by current analyses.	Celgene contest that neutropenia / thrombocytopenia would impact breast cancer and MDS patients equally. However, if the ERG believe that thrombocytopenia and neutropenia cause severe symptoms and wish to test a plausible impact on utility for such severe symptoms we would suggest that this should only apply to patients who were severe enough to receive treatment rather than to all patients experiencing the adverse event.	This is not a factual error. The ERG acknowledges that different scenarios could have been explored. Given the information available regarding occurrence of AE and percentage treated (see also pg 80 ERG report), the ERG decided to explore the scenario of 25% utility decrements to all patients.

Issue 11 Overestimate of impact of double counting in the utilities in sensitivity analysis – alternative suggestion for ERG consideration

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Page 92 "Therefore, an additional scenario was incorporated by the ERG that applied the utility value of Szende for the reduced transfusion state [0.77 sd 0.21]. This scenario increased the ICER to £59,274.	We suggest that a more appropriate analysis might have been to explore the impact of removing the utility decrements for adverse events. This avoids the potential double counting rightly highlighted by the ERG for both patient populations (transfusion independent and transfusion dependent) without assigning	It would be more relevant to explore removing the utility decrements for adverse events rather than arbitrarily assuming a much higher utility for the transfusion dependent group. Particularly as the decrements apply to very low patient numbers – for example the	This is not a factual error. Clearly, the relevance of exploring certain scenarios may always be open to question. While indeed it may be questioned to what extent the utility value from Szende for

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While it might seem unreasonable to apply the utility value for partly transfusion dependent, this might be justified since utility decrements for adverse events are incorporated in the model”	an unrelated utility to the transfusion dependent group.	IV iron chelation market share is only 6% in the base case model and therefore decrement only applies to 6% of patients receiving iron chelation. The maximum impact these decrements can have in total on the model is to alter the ICER to £62,943 if these are all removed. This is a much lower impact than the £68,357 if the arbitrary utility for reduced transfusion is applied to transfusion dependent patients.	reduced transfusion burden is related to the transfusion dependent population, the ERG pointed out (e.g. p.82, p83) that the transfusion dependent utility values from Szende covered a range of health problems not solely related to transfusion dependence. Thus, we still consider our scenario as relevant.