Single Technology Appraisal – Lenalidomide for multiple myeloma

Response to Centre for Health Technology Evaluation (request dated December 1st 2008)

1. Could you provide us with details of how you have calculated your estimates of the cost effectiveness of lenalidomide with the price capping scheme. This does not appear to have been calculated in the updated economic model you sent with your response.

The calculations pertaining to the price capping scheme have been carried out using the updated economic model that was submitted with no change in structure or assumptions other than the lenalidomide cost which is set to zero (no cost) beyond 2 years (26 cycles). This is the only cost item that is affected by the pricing scheme. All other costs, such as routine visits and lab tests are still included over time. To facilitate your review we have subsequently (Monday delivery by hand to NICE) provided you with a copy of the model with the capability for undertaking the price capping analyses enabled.

2 For all analyses please state clearly all assumptions, and detail any inputs that have been changed between the ICER without the scheme, and the ICER with the scheme. For example, please confirm whether any costs that would be expected to be incurred by the NHS beyond 24 months of treatment with lenalidomide, such as for the management of adverse effects due to lenalidomide and follow up appointments, have been included. Please also clarify what assumptions have been made regarding operational costs to the NHS of administering the price capping scheme.

There is no change in any assumptions or inputs in the analyses of the price capping scheme. The only difference is that the cost of lenalidomide drops to zero in any patients who continue treatment beyond 24 months. All other costs, including those of routine management of patients (including monitoring tests and regular physician visits) and of management of adverse events, continue unabated. Therefore, the potential cost burden to the NHS due to routine patient follow up beyond 2 years was accounted for in the pricing scheme analyses. No additional expenses to the NHS for administering the scheme are expected.

It should be noted that the risk of an adverse event drops to zero beyond 2 years in accord with the MM-009&010 clinical trial data. As detailed in the full submission, adverse events occurred shortly after the initiation of treatment in the trials and the rates declined over time with no significant events occurring after 2 years.

Lenalidomide is structurally related to thalidomide (a known human teratogen), if lenalidomide is taken during pregnancy, a teratogenic effect cannot be ruled out and for these reasons a risk minimisation plan (RMP) was mandated and approved by the EMEA and MHRA during the licensing. We propose to implement the price capping scheme through the existing RMP. As an appendix to our response to the ACD we supplied a copy of a letter that we sent to the Department of Health explaining how the price capping scheme can be implemented through the RMP. Following their initial review of our proposal, the Department have asked us to consider implementing the price capping scheme using the existing paper based system with the option of migrating to a web based system in the future. The RMP includes a simple one page Prescription Authorization Form (PAF), which must be completed by the prescribing physician and checked by the dispensing pharmacist every time a prescription for lenalidomide is dispensed for a cycle of treatment. We propose to implement the price capping scheme by adding a single step to the existing RMP, which will simply involve the pharmacist either faxing (free phone number) or posting (pre-paid mailbox) a copy of each PAF to Celgene. The scheme will be administered by Celgene with no additional administrative burden on pharmacists. Unlike existing schemes there will be no need for pharmacists to apply for rebates for non-responders. Instead, patients responding to and benefiting from long-term treatment (after two years) will automatically be provided with treatment free of charge for as long as they remain on treatment. Therefore, we believe that the scheme will have no additional administrative burden on the NHS and we have assumed no operational costs. We understand that the Department is currently consulting with NHS stakeholders on the practicality of administering the scheme within the NHS and we anticipate that this consultation will validate our assumption of no additional administrative burden on the NHS.

3. Could you provide us with details of the number of people in the trial who had not relapsed at 24 months (in the original treatment arm and following crossover) and details of how many further cycles of lenalidomide were required. Could you please provide us with the mean per patient cost for lenalidomide with and without the price capping scheme.

The most accurate estimate of the number of patients receiving lenalidomide longer than 24 months is obtained from the model because the duration of treatment is estimated for every patient while in the clinical trials, many patients are censored due to patients withdrawal from the trials and the limited follow up of the trials to date. This makes the estimate of treatment duration from the trials less reliable than that from the model. The model indicates that 17% of patients with two or more prior therapies will remain progression-free, and thus on treatment, at two years. This proportion drops by about one third in those having already received thalidomide.

Patients still on lenalidomide at 2 Years – model estimate

2+ Prior	17%
2+ Prior (Thal)	11%

Mean Treatment Duration (months) by Time Horizon – model estimate

	2 Years	Lifetime	Mean number of additional cycles beyond 2 years
2+ Prior	11.91 months	13.85 months	2.1
2+ Prior (Thal)	10.38 months	11.25 months	0.9

The model also provides estimates of the average drug costs per patient with and without the price cap:

Mean total drug costs per patient

	No Cap	Cap
2+ Prior	£58,015	£50,787
2+ Prior (Thal)	£47,485	£44,098

We have received feedback from clinical experts in the UK who have informed us that they have patients who continue to receive lenalidomide at 5 years and beyond. We encourage you to seek advice from UK clinical experts on potential treatment durations with lenalidomide.

Thus as well as offering reduced cost burden for nearly 1 in 5 patients the scheme with a cap at two years offers the NHS an insurance against the potential very long-term use of lenalidomide in patients who continue to benefit from the treatment and as a result enjoy a longer life.

4. If using a model to extrapolate the relapse rate on lenalidomide beyond 24 months please provide us with details of how closely the model predicts the trial results.

The economic model used observed progression times for patients who were observed to progress in the course of the clinical trial. For patients not observed to have progressed, a relapse time was predicted from a time-to-progression equation derived from the trials using relevant patient characteristics (as explained in our original submission). Thus, the model uses both observed and predicted progression times. We validated the fit of the prediction equation by showing that the median predicted time was very close to the observed median time, as derived from a Kaplan-Meier analysis. The closeness of fit was also noted in the ERG report (p. 81), where it is stated that the “modelled TTP is reasonably close to that experienced in the MM RCTs”.

In the economic model, the time of progression — and thus of stopping lenalidomide — is estimated only for patients who had not progressed on lenalidomide in the clinical trials (if there was an observed time of progression, this was used directly).

As noted by the ERG on page 81 of their report "modelled TTP is reasonably close to that experienced in the MM RCTs". Indeed, the model matches the trial data very well.

	Median TTP	
	Predicted by model	Observed in pooled trials
One Prior – Len+Dex	14.1 months	14.3 months
Mult. Prior – Len + Dex	9.5 months	9.5 months

5. Whilst I note you have set out in your response reasons why you do not agree with fitting the dexamethasone overall survival curve to the mean from the MRC trial, I would draw your attention to section 4.9 of the ACD, which highlights that the Appraisal Committee considered this approach was valid and would result in more plausible estimates of cost effectiveness than using the median. Could you please provide us with an analysis (both with and without the proposed scheme) using the mean of the overall survival data.

We strongly disagree with using the mean overall survival to calibrate our predictions to the MRC data, and do not believe that the results this would yield are scientifically valid.

As we stated in our response to the ACD, the analyses carried out by the ERG to replicate our calibration to the median appears to be incorrect as the plotted survival curve fails to hit the MRC median. Thus, the relative plausibility of the two approaches (median vs. mean) cannot be inferred from the ERGs analysis. Indeed, calibrating to the mean has several limitations that cast doubt on its validity purely on methodological grounds. We elaborate on a number of reasons in our response to the ERG, chief among which are the following. The primary purpose of the calibration was to remove the effect of cross-overs, which would occur early on in the overall survival curve. As illustrated in the plot produced by the ERG (Figure 6), however, calibration to the mean is more influential in the tail of the distribution. Therefore, by calibrating to the mean, survival in the early portions of the curve would remain unduly influenced by cross-overs. Another methodological concern is the exponential shape of the observed survival in the MRC data. Although this was found to fit the data most closely, it is known that mortality accelerates with time. A distribution that fails to capture this acceleration would tend to overestimate the mean survival time, but the median is less likely to be affected (since it occurs prior to the acceleration of the hazards).

For these reasons, using the median for calibration is more methodologically sound than using the mean. In fact, when adjusting the Len/dex survival the ERG calibrated to the median not the mean (pg 82); and in their discussion of the TTP suggest calibrations to the median from the trials (pg 85).

We would not wish to provide analyses that are based on what we believe to be a methodologically flawed approach and strongly propose that calibration to the median is used for this analysis.

6. When responding to this clarification letter with your updated analyses please note that we cannot accept the entirety of the details of the proposed price capping scheme and related ICERs to be marked as confidential. If NICE is requested by the Department of Health to appraise lenalidomide within the proposed price capping scheme, it will be necessary for sufficient information to be available in the public domain to ensure transparency in evidence, decision making and recommendations. If your response still contains any confidential data, two versions of your response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed. We also ask you to complete the attached checklist for in confidence information.

Thank you for providing further clarification on your interpretation of "sufficient information". At this stage we request that all details regarding the price capping scheme continue to be treated as commercial in confidence. We understand the need for making "sufficient information available in the public domain to ensure transparency in evidence, decision making and recommendations". Therefore, prior to the

appraisal reaching the next stage of publication we would be happy to liaise with NICE to agree the details that are to be made public.