Single Technology Appraisal – Lenalidomide for multiple myeloma

Responses to outstanding clarifications points raised by the Evidence Review Group

Important overriding considerations:

C1.   We note that the model is heavily reliant on hard-coded random numbers. Please could you explain how these were generated, and on what rationale the particular simulation that is presented as base case was chosen? We note that, when we use a different set of random numbers, model outputs change substantially. The submission states that it is necessary to report the average of multiple replications (p. A40). Are we correct to conclude that the base case provided disregards this requirement? The submission also states that model replications "should be carried out manually" (p. A40). Is it suggested that these steps should be performed by the reviewers? If so, on what basis are the model outputs reported in the submission justified?

The model initially submitted had hard-code random numbers in order to ensure a stable base case. These were generated by simply using the =rand() function in excel and then copy and pasting the resulting numbers as values. The fully stochastic model was not submitted initially because we were asked to use only "standard software" either Excel or Data. The fully stochastic model has now been submitted, which has the facility to automatically run multiple replications.

C2.   We are unable to comment on the adequacy or otherwise of methods used for probabilistic sensitivity analysis, since the model provided is not equipped to perform the calculations described in Appendix 14. In order to investigate this important aspect of the submission, could you please provide us with access to a full, functioning version of the model.

The fully stochastic model with Crystal Ball to facilitate PSA has now been submitted.

C4.   P A41: "The model randomly selects patients from the appropriate patient file…" We need some way of verifying this process: is it possible to provide the raw source files? It would be helpful to know the number of trial patients on which each simulation was based, and their demographic and clinical characteristics (i.e. the pool from which each bootstrapping was performed). We also request details of the demographic and clinical characteristics of each simulated cohort.

The source files were included in the model initially submitted (and they remain in the fully stochastic model that has been submitted subsequently). Those excel worksheets with "Patient File" in their names have the raw patient level data. The patients are randomly selected using columns A, B, C on worksheet. The random selection can be verified in the fully stochastic model by pressing F9. Each time that F9 is pressed the selection of patients' changes randomly. Since every simulation is based on trial patients, the number of patients from the trials is always equal to the number simulated. The demographic and clinical characteristics of the randomly

selected patients can be verified by examining those patients that have a 1 in any of columns A, B, and C on each "Patient File" worksheet. Necessarily these will change randomly every time the model is run.

C5.   P A41: Patients are bootstrapped "based on the response distribution for each treatment. For example, if a total of 1,000 patients are to be simulated and 10% had a complete response with treatment A, then the model randomly picks 100 patients from the CR file and assigns them to treatment A." We note that, in the model, the numbers of simulated patients do not precisely reflect the proportions specified in the submission (and, as a further check, do not sum to 1000 per arm). Could you clarify the explanation for why this is the case?

The actual number of patients randomly selected in each run may vary slightly from the desired number in each response level, and thus the total may vary from 1,000, because the process is stochastic. The random selections are set to on average select the desired number, but in any one run there may be slightly more or less patients whose random number is below the selected %.