The Royal College of Pathologists
Pathology: the science behind the cure

# Lenalidomide for multiple myeloma in people who have received at least one prior therapy

**Name:** [redacted]

**Organisation:** Royal College of Pathologists, BSH, UKMF and RCP

## Response to ACD

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

Yes

2) **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 are pleased that the committee have concluded that lenalidomide/dexamethasone combination therapy improves outcomes in people with relapsed multiple myeloma. We are concerned, however, that there appear to be several mis-interpretations of the evidence, leading to potentially unsound conclusions, all of which would serve to increase the cost per QALY unjustifiably.

A) A fundamental mis-interpretation of the clinical trial data by the ERG is presented on page 87 of the report by the Peninsula technology Assessment Group. This relates to "uncertainties" over the overall survival of patients treated with Dex. Here it is stated that, because the recent report from the Mayo group indicated that the improved survival of patients with multiple myeloma today is because of the advent of new therapies, therefore the overall survival of patients treated with Dex may be better than calculated from the MRC data. The group conclude, we believe without justification, that therefore it would be better to "populate the cost-effectiveness model with data for Dex taken from MM-009 and MM-010 with patients who crossed over to Len censored". This demonstrates a fundamental misunderstanding of the trial structure and rationale – and amounts to suggesting that the comparator arm consist of patients who start treatment with Dex, then switch to Len/Dex!! To re-iterate, the improvement in survival of patients in the last decade is due to the use of

new therapies, including Bortezomib and lenalidomide, and hence for patients treated on Dex alone (the comparator arm), no such improvement in survival is expected, and therefore the MRC data are still appropriate to the economic evaluation. It must surely be obvious that using the same treatment for the same disease is not going to lead to a change in response over time given that the fundamental pathology of the disease and the efficacy of the drug remain the same.

B) A second misconception is presented on page 31 of the same report. The authors state that the use of outcome measure to predict OS is "a recurring problem in MM research" and that complete response rate is not valid surrogate for OS, and neither is PFS. This is a problem with the ERG focussing on particular papers rather than reviewing all the relevant literature. Both the papers referenced are from the Little Rock group who have a unique and particularly aggressive treatment protocol for newly diagnosed patients, and the second paper was evaluating the impact of including Thalidomide. The first paper indeed confirms the importance of PFS for OS. Balanced against these papers is a wealth of data from thousands of myeloma patient cohorts that confirms that depth of response, i.e. CR rates, predicts for PFS and OS. Some examples are given below including the paper in the NEJM reporting on the UK MRC-sponsored Myeloma VII trial:

1. Child JA et al. ,NEJM, 2007, 348:1875
2. van de Velde et al, Haematologica, 2007, 92:1399
3. Lahuerta et al, J Clin Oncol, 2008, Epub
4. Niesvizby et al, Brit J Haematol, 2008, 143:46

The last relates to patients in the relapsed setting.

D) The evaluation by the ERG of the ICER using Bortezomib as comparator for patients with only one prior therapy took the maximum number of cycles to be 11, whereas the median number of cycles received by patients in the APEX trial was 7. Eleven cycles was the maximum allowed for patients who achieved CR.

E) 3.17. The ERG commented that the costs of routine medical management assumed in the model are too low. Whilst we have no specific expertise in health economic analysis technology, we wish to point out that, given the better toxicity profile of the technology (see Section 4.6), it would be hardly surprising that these costs would be lower than the figures accepted in the appraisal of bortezomib. In addition we would like to make clear that G-CSF is seldom used in the UK and Europe for the management of adverse effects of bone marrow suppression and in clinical practice most clinicians would reduce the dose of lenalidomide according to the SMPC. An important point to make is that the incidence of neutropenic infections in the MM-009 and MM-010 studies was very low (1.7%). This has been borne out

by subsequent clinical experience and is what informs clinicians' judgement that GCSF is not usually needed. Finally, anti-thrombotic prophylaxis can be effectively achieved with low dose aspirin in >90% of patients on Lenalidomide / dexamethasone, and the cost of warfarin or low molecular weight heparin in the remaining 5% is negligible (no additional outpatient attendances would be required for monitoring of INR over and above regular outpatient attendances). This policy will be incorporated in the new national Myeloma guideline being developed by the UKMF.

F)The committee comment that there is uncertainty in the results of the indirect comparison (4.5). Such uncertainty is inherent in the issues around treating relapsed and refractory myeloma, because of the nature of the necessary ethics of the studies which inform the process and also the pace at which the therapeutic options are evolving, e.g. the current practice of using Bortezomib with dexamethasone.

G) We are pleased that the committee noted that lenalidomide has a more favourable adverse effect profile, and is particularly useful for patients with pre-existing neuropathy, in whom the use of bortezomib is restricted (4.6). We argue that the increased risk of venous thrombosis and embolism is effectively prevented by the use of low dose aspirin in the majority of patients, and for the small minority who require warfarin or low-molecular weight heparin, the additional costs would be negligible as such patients would routinely be under regular monitoring for their relapsed disease.

H) We wish to point out that the costs and utility decrements (3.12) are based on a single study of a small number of patients receiving intensive chemotherapy followed by autologous stem cell transplantation, where a utility value of 0.81 is assigned to patients in remission, and a value of 0.64 assigned to those with progressive disease. We note that these values are based on the utility of the general public at a median age of 54 years, and are surprised that the ERG have applied them to the patient population under consideration. Given that the median age at diagnosis is 65 years, patients at first and subsequent relapse would be around 70 years of age, and we consider that the use of utility values based on a healthy population aged 54 years is inappropriate, and constitutes discrimination against an elderly population.

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

Based on the points raised above, we do not feel that the provisional recommendations are sound, nor do they constitute a suitable basis for the preparation for the guidance to the NHS.
We note that the effect of all the points on which we disagree with the ERG would have been to increase the cost per QALY as estimated by the ERG. We believe therefore that the ERG should re-model the cost calculation to take these points into consideration when the effect should be to lower the estimated cost per QALY to a figure which more closely approaches the figure of £30,000, usually considered affordable.
We worry that having identified a number of fundamental misconceptions and misunderstandings in the interpretation of the clinical evidence that similar errors may have occurred in assembling of the economic evidence on which having no specific expertise we are not qualified to comment.

We are also aware that NICE will shortly be bringing out specific guidance to its appraisal committees with regard to life-extending medicines licensed for terminal illnesses affecting small groups of patients. This guidance may be relevant to the technology and, if so, we hope that the committee take this guidance into account before issuing the FAD.

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

Please see the point made above with regard to the older age group of the patients for whom this technology is relevant, and the concern that the current utility values discriminate against this older population.