The Appraisal committee has asked for several points to be commented on:

1. **Has all the relevant evidence been taken into account?**
   
   Our consensus view is that all the evidence that was available when the meeting took place in May was taken into account.

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
   
   There appear to be two differences of opinion. These have arisen because there is no long term data available as yet for the BRIM 3 study on which the analysis was based. The study was too short to provide robust evidence of the overall survival gain beyond the length of the trial.

   The manufacturers argue that there is a continued benefit in the vemurafenib group compared to the dacarbazine group. Whereas the ERG argue that although there is initial benefit in the vemurafenib group both survival curves for vemurafenib and dacarbazine eventually meet and the initial advantage in the vemurafenib treated patients is lost. Calculations were made by the manufacturer using a 'stabilised' hazard ratio representing the differences between the vemurafenib and dacarbazine arms up to a projected 14-month figure.

   The short term nature of the results and the heterogeneity of the patient population has led to substantial uncertainty when projecting long-term benefits of treatment and therefore it is difficult to make firm conclusions on cost effectiveness without these.

   These uncertainties should be taken into account.

   Also because the interim analysis in the BRIM3 study showed significant benefit in the vemurafenib arm, patients on dacarbazine alone crossed over to vemurafenib making long term conclusions in the control arm difficult. Also those patients initially that were in the BRIM 3 study on dacarbazine that progressed may well have gone onto have other treatments that are currently under investigation including ipilimumab making analysis of their long term survival difficult.

   This essentially means that the data on overall survival from the October 2011 data cut-off was confounded both by crossover and by patients progressing on dacarbazine prior to cut off being offered other experimental treatments.

   As there is considerable uncertainty as to whether people who received vemurafenib would maintain a significant long-term survival benefit over those who received dacarbazine and about the magnitude of the benefit it is difficult to conclude objectively on the statistical analysis.
It should also be taken into consideration that vemurafenib treatment can be so effective within a short space of time that it does allow patients to go back to their ‘normal’ lives including work which in itself has an economic value not taken into account in these calculations.

3. *Are the provisional recommendations sound and a suitable guidance basis for guidance to the NHS?*

   This is a novel and innovative treatment that can be regarded as a step-change in the management of patients with metastatic melanoma. Due to its quick response rate, tolerability and manageable side effects as well as being an oral medication it will be a medication that physicians and patients will be keen to use.