Eisai

hhc
human health care

Dr Maggie Helliwell
Appeals Committee Chair
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20 December, 2011

Dear Dr Helliwell

Final Appraisal Determination of eribulin for the treatment of locally advanced or metastatic breast cancer

Thank you for your letter dated 7 December, providing your preliminary views of the points of appeal set out in our Notice of Appeal submitted on 1 December 2011.

We now provide our response to your initial views, including clarification of the issues we have raised, where this is appropriate.

Ground 1

Point 1.1 The additional data submitted by Eisai in response to the ACD were substantial and the Appraisal Committee's conclusions in relation to this material should have been subject to consultation.

Noted.

Point 1.2 The late disclosure of the supplementary report prepared by the ERG precluded proper consideration of the report by Eisai prior to the second meeting of the Appraisal Committee.

Noted.

Point 1.3 The Appraisal Committee's approach to the estimation of the overall survival benefit associated with eribulin is not consistent with standards identified by the Decision Support Unit and the choices which form the basis for the estimation are unexplained and lack transparency.

You say in your letter that you have been unable to find any record of Eisai having suggested that the methodology used by the ERG and accepted by the Appraisal Committee was unfair, when responding to the ACD. However, Eisai commented in detail on the economic modelling carried out by the ERG and accepted by the Appraisal Committee in the Appendix to its ACD response, entitled "Additional Evidence in Response to the Appraisal Consultation Document (ACD)", which may not have been provided to you. All of the issues raised at point 1.3 of our appeal were previously the subject of comment in within the Appendix to our response to the ACD.

- At page 5 of the Appendix, Eisai referred to the recommendations of NICE's Decision Support Unit (Latimer et al) and the fact that, contrary to the DSU's overview of the approach to the estimation of overall survival, the ERG had chosen to rely upon one of the least common and non-

standard methodologies for the estimation of overall survival associated with eribulin (example (a) of point 1.3 of Eisai's appeal). No explanation for selecting this methodology was provided.

- At page 7 of the Appendix, Eisai noted that, while the ERG had used an exponential curve to estimate overall survival "the choice of this functional form was not explained and does not seem to relate to the functional form which fits the data" (example (b) of point 1.3 of Eisai's appeal).

- At page 5 of the Appendix, Eisai commented in relation to the importance of determining the point at which the parameterised curve should be applied and the fact that the "decision made by the ERG about where the non-parametric curves stops and the parametric starts was arbitrary and sensitivity analysis is not fully explored (example (c) of point 1.3 of Eisai's appeal).

- At page 8 of the Appendix, Eisai refers to the fact that the ERG hypothesised that the survival curve based on the trial data had stabilised at 100 days post randomisation and that the exponential curve used by the ERG to estimate overall survival is based at this point (example (d) of point 1.3 of Eisai's appeal) . No explanation is provided to justify the 100 days cut off and we commented that the results of the estimation are sensitive to this assumption, which have not been explored or investigated by the ERG through sensitivity analyses.

In summary, Eisai's response to the ACD made clear our concerns regarding the methodology used by the ERG to estimate overall survival including the fact that this did not comply with NICE's DSU's recommended approach and that choices made by the ERG during the estimation, which exert a substantial influence over the results, were unexplained.

Point 1.4 The Appraisal Committee has failed to consider a comparison of eribulin with TPC in the population of patients previously treated with capecitabine.

Noted

Point 1.5 The Appraisal Committee has not placed adequate weight on the innovative nature of eribulin in the context of this appraisal.

You say, in your letter, that the adequacy of the weight given to a particular consideration cannot be a matter of fairness to be determined under Ground 1 and suggest that this point of appeal should not be referred to the appeal panel.

As you know, Directions issued by the Secretary of State and reflected in NICE's procedures, require the Institute to take into account "the potential for long term benefits to the NHS of innovation", when formulating its guidance. However, as noted in the reports prepared by Sir David Cooksey and Sir Ian Kennedy, concerns have been expressed that NICE does not adequately consider the innovative nature of technologies under appraisal, when formulating its guidance. In this case, while eribulin has a novel mechanism of action and demonstrates a step-change in the treatment of patients with locally advanced or metastatic breast cancer, at this stage in the treatment pathway, there is, as indicated in our appeal letter, "no indication in the FAD that the Appraisal Committee gave any consideration to the innovative nature of eribulin either in the context of the appraisal overall or when particularly considering the application of the end of life criteria".

Failure to follow the Secretary of State's Directions and NICE's procedures is clearly a valid point of appeal under Ground 1. Furthermore, in view of the concerns which resulted in the Cooksey and Kennedy reports, we suggest that there is a high public interest in the Appraisal Committee's

consideration of innovation being subject to scrutiny by the Appeal Panel, in cases where it has been called into question.

Point 1.6 The Appraisal Committee's conclusions with respect to the costs of vinorelbine which should be used for economic modelling in this appraisal are inconsistent with the approach specified in NICE's procedures and unfair.

We note that you agree this is a valid appeal point under Ground 1.

However, we should be grateful if you would please clarify your comment that "inconsistency with NICE's procedures is no longer a ground of appeal".

Point 1.7 The Appraisal Committee's repeated criticisms of the comparisons of eribulin with individual TPC failed to take into account that these were required by the SCOPE and are therefore unfair.

We note your comments in relation to this point of appeal and are content to suggest some additional wording to the Guidance Executive that would, we believe, clarify the position and resolve our concerns.

Ground 2

Point 2.1 The Appraisal Committee's conclusions with respect to the adverse events associated with eribulin do not reflect a balanced and reasonable assessment of the available evidence.

Noted

Point 2.2 The Committee's decision to reject the analysis based on the data from Region 1 of the EMBRACE trial is unreasonable.

Noted

Point 2.3 The Appraisal Committee's reliance on the calculation of overall survival for patients pre-treated with capecitabine, based on the ERG's methodology set out in its addendum report, is unreasonable.

Noted

We hope our additional submissions, set out above, have clarified the issues raised in our appeal and we look forward to receiving your final decision on admissibility. However, in the meantime, if we can provide any further assistance in relation to our appeal, please let us know.

Yours sincerely

Mr Nick Burgin
European Director of Market Access