Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

30th November 2011

Dear Sir/Madam

Re: FINAL APPRAISAL DETERMINATION OF ERIBULIN FOR THE TREATMENT OF LOCALLY ADVANCED OR METASTATIC BREAST CANCER

Eisai Ltd would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following grounds:

Ground one: The Institute has failed to act fairly

Ground two: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted.

If you require any further information or clarification then please do not hesitate to contact us.

Yours faithfully

Nick Burgin
Managing Director

NICE APPRAISAL OF ERIBULIN FOR THE TREATMENT OF LOCALLY ADVANCED OR METASTATIC BREAST CANCER

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION BY EISAI LIMITED

EXECUTIVE SUMMARY

Eisai's appeal is advanced under Ground 1 (procedural unfairness) and Ground 2 (unreasonableness) of the grounds permitted in accordance with NICE's Guide to the Technology Appraisal Appeal Process.

Ground 1 (Procedural Unfairness)

- While Eisai submitted substantial new data in response to the ACD, the conclusions of the ERG and the Appraisal Committee have not been subject to consultation.

- The late disclosure of the Addendum Report prepared by the ERG precluded proper consideration of the report by Eisai or submission of written comments to the Appraisal Committee prior to its second meeting.

- 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 calculations are unexplained and lack transparency.

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

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

- The Committee's conclusions with respect to the costs of vinorelbine are inconsistent with the approach specified in NICE's procedures and unfair.

- The Appraisal Committee's repeated criticisms of the comparisons of eribulin with individual TPC fail to take into account that these were required by the Scope.

Ground 2 (The Committee's conclusions are unreasonable)

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

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

- 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.

INTRODUCTION

Eisai Ltd is responsible for the UK supply of eribulin (Halaven), authorised under the centralised procedure by the European Commission on 17 March 2011, following a positive opinion by the Committee for Medicinal Products for Human use (CHMP) on 21 January 2011. Eribulin is indicated "*for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments*."

HISTORY OF THE APPRAISAL

Eribulin was referred for Single Technology Appraisal in late 2010.

The Final Scope was issued in January 2011, setting out the remit for this appraisal: " *To appraise the clinical and cost effectiveness of eribulin within its licensed indication for the treatment of people with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease*". The comparator technologies identified in the Scope were vinorelbine, capecitabine and gemcitabine.

Eisai provided its submission for the STA on 11 March 2011. That submission included a patient access scheme for eribulin, approved by the Department of Health. The Liverpool Reviews and Implementation Group (LRiG) were appointed as the Evidence Review Group (ERG) and prepared a report in relation to Eisai's submission dated 24 May 2011.

The first meeting of the Appraisal Committee to consider eribulin took place on 23 June 2011 and an Appraisal Consultation Document (ACD) was issued for consultation on 14 July 2011. The ACD stated at paragraph 1.1: "*Eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease*".

Eisai submitted its response to the ACD on 9 August 2011, with additional evidence provided as a result of the preliminary conclusions of the Appraisal Committee on 19 August 2011. The ERG produced an Addendum to its report considering these new data dated 13 September 2011.

The second meeting of the Appraisal Committee took place on 27 September 2011 and the Final Appraisal Determination (FAD) was issued on 10 November 2011. The conclusions at paragraph 1.1 of the FAD were unchanged from those set out in the ACD.

GROUNDS OF APPEAL

Eisai's points of appeal in relation to the FAD are set out below under the grounds permitted by NICE.

1. Ground 1: Procedural Unfairness

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

Following the comment by the Appraisal Committee at paragraph 4.5 of the ACD, Eisai submitted data from the EMBRACE trial in relation to the effects of eribulin in patients who had previously been treated with capecitabine (74% of the trial population- 554 patients). These data were accepted by NICE and were the subject of an Addendum Report by the ERG. However despite the fact that the new analyses of eribulin in patients previously treated with capecitabine were the subject of substantial consideration in the FAD, the data submitted by Eisai, the Report prepared by the ERG and the conclusions of the Appraisal Committee have not been subject to consultation.

Paragraph 3.5.35 of the STA Guide indicates that the Centre Director and the Chairman of the Appraisal Committee will decide whether it is necessary to prepare a second ACD in circumstances where comments and/or new evidence submitted in response to consultation, lead to "*a substantial revision of the ACD, involving a major change in the recommendations, considerations and/or evidence base*". It is Eisai's case that the additional data submitted in response to the ACD in this case, involving a new analysis and requiring an Addendum Report by the ERG, constituted a major change to the considerations and evidence base in this appraisal and that it was accordingly unfair to proceed to issue a FAD without submitting this new material to consultation and taking into account the responses of all consultees, including patient groups and professional bodies as well as the manufacturer.

It would be inappropriate for Eisai to address in this appeal what the outcome of consultation might have been, had it been undertaken. However, by way of example only, we identify below certain issues where we believe the Committee would have derived particular benefit from the views of consultees and commentators:

- The FAD expresses strong criticisms of Eisai and the supplementary analysis which was submitted by us and accepted by NICE following the ACD. We do not believe these criticisms are justified and consider that it is unfair to issue guidance containing such criticisms without allowing Eisai an opportunity fully to respond to them.

- Eisai disagrees fundamentally with the approach followed by the ERG in its Addendum Report and accepted by the Appraisal Committee, including in relation to the calculation of overall survival associated with eribulin therapy in patients who have received pre-treatment with capecitabine, and with the conclusion that the survival of patients receiving eribulin and vinorelbine may converge after 2 years (paragraphs 4.13 - 4.14 of the FAD). However there has been no opportunity for Eisai, clinical experts or patient bodies to refute the conclusions of

the Appraisal Committee which are based upon it. This omission is unfair and represents a procedural flaw in this appraisal.

- The supplemental data submitted by Eisai in response to the ACD included consideration of patients who have previously been treated with capecitabine and compared eribulin with either vinorelbine (Eisai's preferred comparator) or TPC. While the Appraisal Committee has criticised the comparison of eribulin with vinorelbine, it has failed to consider the comparison with TPC and consultation would have allowed consultees and commentators to explain to NICE, outside the appeal process, why this omission was inappropriate and unfair.

In summary, consultation is necessary to ensure that the Appraisal Committee has fully considered important issues and has taken into account the views of stakeholders before guidance is finalised. In this case, the additional analyses constituted a substantial change in the focus of the appraisal and the consideration of the issues by the Appraisal Committee. This was recognised by the Committee at paragraph 4.11 of the FAD, where they refer to this material as a "new decision problem". In these circumstances we strongly believe that failure to permit consultation on the additional analyses submitted by Eisai, the Addendum Report prepared by the ERG and the new conclusions by the Appraisal Committee was inconsistent with a fair procedure.

Remedy: Eisai requests that the appraisal is returned to the Appraisal Committee and the current FAD issued as a second ACD to consultees and commentators for consultation before the Committee's conclusions are finalised.

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.

As indicated in the previous point of appeal, an Addendum Report, dated 13 September 2011, was prepared by the ERG in relation to the additional analyses submitted by Eisai in response to the ACD. This was disclosed to Eisai on 20 September 2011, for the purpose only of identification of factual errors, in advance of the Committee's meeting on 27 September. When the Addendum Report was provided to Eisai, NICE stated that it would not be possible to make any amendments to the Report or send errata to the Committee before its meeting on 27 September and that Eisai's written comments on the Report would not be provided to the Committee.

The procedure followed was therefore inconsistent with paragraph 3.4.11 of the STA process guide which indicates that manufacturers will have 5 working days in which to submit factual errors to NICE and that the Institute will prepare a document highlighting these for the Appraisal Committee meeting. This is unfair. In particular, the supplementary report prepared by the ERG was unbalanced, misleading and contained certain factual errors. We raised these issues with NICE in a written document submitted before the second meeting of the Appraisal Committee, however the fact that our

comments were not available to the Appraisal Committee in a written form in advance of their meeting, is procedurally unfair. In particular, it is unclear whether the Committee was appropriately advised of all or any of the matters raised by Eisai in response to the ERG's Addendum Report and, even if they were advised of such matters, it seems that this was not in documentary form and that inadequate time was available for consideration of these matters in advance of the hearing.

In the context of Eisai's particular concerns regarding the content of the ERG's Addendum Report, set out in the document submitted to NICE on 20 September 2011, and the fact that this was relied upon by the Appraisal Committee in formulating the conclusions in the FAD, we believe the failure to permit adequate consideration of the Report by Eisai prior to the second meeting of the Committee or to follow the defined process in relation to submissions on factual errors, has substantially prejudiced the outcome of this appraisal.

Remedy: Eisai requests that the appraisal is returned to the Appraisal Committee for further consideration and that the consultation referred to under point 1.1 above should include the additional data submitted by Eisai and the ERG's Addendum Report.

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.

In their original Report dated 24 May 2011, the ERG used a method, developed by themselves (referred to as the "LRiG exponential method") to estimate overall survival associated with eribulin treatment and with TPC. The ERG's methodology was accepted by the Appraisal Committee when it first met to consider eribulin on 23 June 2011 and in the ACD subsequently issued on 14 July 2011.

The novel approach developed by the ERG does not represent standard methodology; it is a hybrid method incorporating aspects of other strategies. Applying its methodology to this appraisal, the ERG truncated the Kaplan Meier curves at the date of the last recorded trial event (a death in a trial where the primary outcome measure is overall survival) to eliminate the effects of the tails of the distribution (paragraph 3.31 of the FAD) and then attached exponential curves to the truncated Kaplan Meier curves to project survival trends to the end of life (paragraph 3.32 of the FAD).

However, the use of the LRiG exponential method in the way proposed by the ERG and accepted by the Appraisal Committee in this appraisal is not consistent with the approach recommended by NICE's Decision Support Unit (DSU). Furthermore, decisions made in estimating overall survival using this method are unexplained and appear arbitrary. Eisai refers to the following matters in particular:

a) The decision by the ERG and Appraisal Committee to rely upon the LRiG methodology for extrapolation of overall survival does not follow the approach recommended by NICE's Decision Support Unit (DSU)

NICE's DSU is commissioned by NICE to provide a research and training resource to support the Institute's Technology Appraisal Programme. It has therefore prepared a series of Technical Support Documents which are intended to complement NICE's Guide to the Methods of Technology Appraisal by providing detailed information on how to implement specific methods. While these Technical Support Documents do not form part of NICE's process guides, in circumstances where the Technical Support Documents are commissioned by NICE and prepared by the Institute's DSU, the Appraisal Committee should have sound reasons for departing from the recommended methods.

A DSU Technical Support Document entitled "Survival Analysis for Economic Evaluations alongside Clinical Trials - Extrapolation with Patient-Level Data", was prepared in June 2011 ("the DSU Report"). This provides a detailed overview of methods employed in survival analysis in appraisals conducted by NICE, including the following statements:

- "*Parametric models should be used, rather than restricted means approaches, unless data is almost entirely complete*" (page 39)

- With respect to the choice of methodology, *"whatever approach is taken should be systematically justified in comparison to alternative approaches and assumptions, and the robustness of results to these alternatives should be considered"* (page 41).

The DSU Report confirmed that the proportional hazards methods (section 4.1.3, page 31) and a method where parametric extrapolation techniques are applied to both arms of the trial (section 4.1.2, page 29) are established methods and stated that a range of standard approaches should be attempted to demonstrate that the choice of model has not been arbitrary. It is only where these standard approaches "*appear unsuitable ... the use of piecewise modelling and other novel survival modelling methods ... should be considered*" (page 38).

In considering eribulin, the Appraisal Committee justified its decision to reject the proportional hazards method proposed by Eisai, based on a supposed declining proportional effect, however no attempt was made to consider a non-proportional method which employed a parameterisation of both arms of the trial. By ignoring alternative established methods and proceeding directly to use the LRiG Exponential Method (a piecewise modelling approach, described as "novel" by the DSU at section 4.1.5 of its Report), the ERG and Appraisal Committee have disregarded the standards identified by NICE's DSU. In circumstances where these standards are

those commissioned by NICE and developed by NICE's DSU, consultees are entitled to expect that they will be followed by the Appraisal Committee, unless there is a good reason for diverging from them. However in this case the Appraisal Committee has provided no explanation for failing to follow the approach set out in the DSU Report.

b) The Appraisal Committee has provided no explanation for using an exponential curve to estimate overall survival.

Where piecewise models are used, it is essential that an appropriate parametric curve is used to extrapolate the trial data. The DSU Report states that a range of parametric models should be considered (page 13).

In this case however, the ERG has seemingly considered only an exponential curve and has disregarded other functional forms. No reasons have been given by the ERG to explain its approach, despite the DSU's view that *"whatever approach is taken should be systematically justified ...*" (page 41) other than the bald statement at page 74 of its report that the cumulative mortality hazard plots from EMBRACE "*reveal long-term linear trends for both eribulin and TPC beyond the first 3 to 4 months of the trial, indicating that exponential survival functions would be appropriate for projecting OS beyond the available data*". The statement in the ERG's report does not represent systematic justification and does not attempt to explain choice of an exponential curve in circumstances where this does not provide the best fit to the data.

c) The ERG's decision, accepted by the Appraisal Committee, to attach the parameterised curve to the very end of the non-parametric curve, where the data are more uncertain, is unexplained

The estimation of overall survival using the LRiG Method is likely to be highly sensitive to the point at which the parameterised curve is attached to the Kaplan Meier curve, where the analyst assumes that subsequent data from both arms of the trial will be proportional in the same relationship. It is therefore necessary, as recognised in the DSU Report, that if the ERG uses the LRiG approach, it provides a sound justification for the transfer point.

The DSU Report states, "*Both the Gelber method and the LRiG exponential method are likely to be sensitive to the point at which the parametric model takes over from the Kaplan Meier and therefore if either of these methods are used it is important to provide a clear rationale for the switch point using statistical analyses*" (page 35).

In this appraisal, the ERG has attached the parameterised curve at day 750 following randomisation (page 74 ERG report) at the end of the Kaplan Meier curve, where there are few events recorded and the data are therefore more uncertain. No explanation is given by the ERG to justify its choice of transfer point, which leads to a smaller estimation of treatment effects than attachment at other points on the Kaplan

Meier curve. The Appraisal Committee accepted the transfer point proposed by the ERG, even though no justification for the 750 days point was provided and in circumstances where alternative transfer points give larger estimations of treatment effects. The lack of transparency in this respect has prejudiced Eisai in its ability to respond to the conclusions of the Committee in this respect and are, accordingly, unfair.

d) The ERG's decision, accepted by the Appraisal Committee, to estimate the exponential parameter values from the post 100 day trial evidence, is unexplained and lacks transparency.

The exponential curve used by the ERG to extrapolate overall survival is based on the EMBRACE trial data from 100 days post randomisation. No reasons have been provided by the ERG to explain the selection of the 100 day cut-off, even though, as stated by the DSU in its Report, the approach followed should be investigated and justified. Furthermore, no sensitivity analyses were carried out by the ERG to investigate the effect of selecting alternative cut-off points, e.g. 90 days or 120 days, to assess the effect of changes on the estimation of overall survival.

In summary therefore, the Appraisal Committee's reliance on the conclusions of the ERG with respect to the estimation of overall survival is inadequately explained and therefore lacks transparency. This has prejudiced Eisai in its ability to respond to the conclusions of the Appraisal Committee and to participate in consultation in relation to this appraisal.

Remedy: Eisai requests that the Appraisal Committee is directed to explain the rationale for the parameters selected for the purpose of estimating overall survival, including the functional form and attachment point, in the context of this appraisal and that Eisai is permitted to respond to these in consultation.

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

The additional analyses provided by Eisai, in response to the ACD, considered the effects of eribulin compared with either vinorelbine or TPC, in patients who had previously received treatment with capecitabine. In our submission, we suggested that the most relevant comparator in the context of current NICE guidelines (NICE Clinical Guideline 81). However, in view of the Appraisal Committee's earlier conclusion that eribulin should be compared with TPC, rather than the individual TPCs included in the EMBRACE trial, Eisai also provided analyses comparing eribulin with TPC in the post-capecitabine population.

However, when the ERG reviewed the additional data submitted by Eisai they gave no consideration to the comparison of eribulin with TPC in patients pre-treated with capecitabine. No reason for this omission is provided in the ERG's Addendum Report, save that the ERG states, at Section 3.1 "*the manufacturer has modified the comparator*

technology from "treatment of physicians choice " (TPC) to vinorelbine, on the basis that this more closely matches the stage within the current NICE guidelines at which it is envisaged that eribulin may be used". The fact that the failure by the ERG to give any consideration to the comparison of eribulin with TPC in this patient population represents a flaw in the appraisal process, was identified by Eisai in its written comments on the ERG's addendum report provided to NICE on 20 September 2011.

As noted in our appeal at 1.2 above, the short time period for consideration of the ERGs Addendum Report and the fact that our written comments on the Report were not placed before the Appraisal Committee, means that it is unclear whether the Appraisal Committee was aware of our concerns in this respect. The Appraisal Committee, like the ERG, therefore fails to consider the comparison of eribulin with TPC in patients previously treated with capecitabine. The Committee gives no reasons for its approach, beyond repeating the statement by the ERG that Eisai had suggested the comparison with vinorelbine would be most appropriate in this sub-group.

Eisai believes the failure by the Committee to consider a comparison of eribulin with TPC in the population of patients previously treated with capecitabine is unfair, particularly in the context of the following statements by the Committee:

- The Committee has previously expressed the view that, when considering the ITT population from EMBRACE, it is appropriate to compare eribulin with TPC, rather than the individual comparative treatments (paragraph 4.5 of the FAD). In the ITT population therefore, the Committee based its conclusions on a comparison of eribulin with TPC even though some individual treatments included in TPC are not those generally used to treat patients with locally advanced or metastatic breast cancer in the NHS. In these circumstances, if the Appraisal Committee believes that a different approach is required when considering patients who have previously been treated with capecitabine, then the Committee should provide the reasons for that conclusion in the FAD.

- The Appraisal Committee expressed considerable concern about the comparison of eribulin with vinorelbine in patients previously treated with capecitabine, in circumstances where the vinorelbine comparator group is small (paragraphs 4.13-4.14 of the FAD) and referred to "*uncertainty around the survival estimates*" (paragraph 4.16) and "*the lack of a robust survival advantage in this setting*" (4.17). It is therefore particularly surprising that the Committee did not consider the comparison of eribulin with TPC, which comprises 74% of the trial population and involves a larger comparator group, consistent with the approach followed in relation to the ITT population.

In summary, we believe that the Committee should have considered both comparisons submitted by Eisai in response to the ACD. The requirement to consider the comparison

with TPC is further heightened by the approach followed by the Appraisal Committee to the ITT population from EMBRACE, and the fact that the Committee was concerned regarding the small size of the vinorelbine comparator group. Furthermore the Appraisal Committee has provided no reasons to justify excluding the TPC comparison.

Remedy: Eisai requests that the appraisal should be returned to the Appraisal Committee with directions to consider a comparison of eribulin with TPC in the population of patients previously treated with capecitabine.

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

Eribulin exerts its anti-cancer effects by interference with the tubulin spindles involved in mitosis (cell division), ultimately leading to cell death. It belongs to the halichondrin class of drugs and is the first product in its class to be authorised.

Directions from the Secretary of State require the Appraisal Committee to take into account "*the potential for long-term benefits to the NHS of innovation*" when formulating its recommendations (paragraph 1.11 of the STA Guide). Furthermore, the supplementary advice on "appraising life extending, end of life treatments" states "*the Institute has taken account of its responsibility to recognise the potential for long-term benefits to the NHS of innovation. In this context, it considers it appropriate for its Appraisal Committees to have regard to the importance of supporting the development of innovative treatments that are anticipated to be licensed for small groups of patients who have an incurable illness*". (Paragraph 1.3).

In January 2009, Sir David Cooksey wrote in his "Review and Refresh of Bioscience 2015" that "*Currently, the perceived problem for UK industry is that NICE appraisals do not operate in a way that is supportive of innovation, or uptake and access to medicines and therefore dissuade companies from investing in the UK"*. The Cooksey Report was followed by a Report prepared by Sir Ian Kennedy for NICE "Appraising the Value of Innovation and Other Benefits". In response to the observations of Sir David Cooksey, Sir Ian concluded "*NICE should build on its reputation as leading the world in the appraisal of products to establish itself also as a world leader in promoting innovation and the early adoption of treatments*".

Despite these statements, Eisai believes that the recommendations of Sir Ian Kennedy's Report and the requirements of NICE's own procedures to support innovation, have not been taken into account in this appraisal. The mechanism of action of eribulin is novel; it is the first medicinal product in its class to be authorised and represents the only treatment licensed for the treatment of advanced and heavily pre-treated breast cancer. However, while the FAD records that the Committee "*heard from the clinical specialist and patient expert that it is unusual for a technology to show an overall survival benefit in advanced breast cancer at this stage of the clinical pathway and also of the importance of having a further treatment option for patients whose previous chemotherapy has failed*", there is

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.

Remedy: Eisai requests that the Appraisal Committee is directed to reconsider this appraisal specifically taking into account the innovative nature of eribulin, both in relation to the appraisal in general and also in the context of the application of the end of life criteria.

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

At paragraph 4.7 of the FAD, the Appraisal Committee reaches various conclusions in relation to the costings used for the economic modelling in this appraisal. In relation to vinorelbine, the Committee expresses the view that the costings used by Eisai in the economic modelling are too high for reasons including that (a) the Committee states that vinorelbine is generally given on days 1 and 8 of a 21 day cycle, rather than once weekly as stated in the SmPC; and (b) the Committee understands from data supplied by the NHS Commercial Medicines Unit, that vinorelbine is available at a range of discounted prices substantially less than the list price.

Eisai believes that these conclusions are inconsistent with the approach to appraisal required in accordance with NICE's procedures, lack transparency or are otherwise unfair.

- At paragraph 4.10 the FAD states that "*the Committee also noted that vinorelbine was available to the NHS with discounts in the region of 80-90% from the list prices (as issued by the NHS Commercial Medicines Unit) which would result in a further increase in the ICERs per QALY gained*".

  However, NICE's procedures provide that discounted prices should not form part of the appraisal unless these are transparent and consistently available across the NHS for a guaranteed period. Paragraph 5.5.2 of NICE's Guide to the Methods of Technology Appraisal states:

  > "*When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the reference-case analysis. Sensitivity analysis should assess the implications of variations from this price. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and can be consistently available across the NHS, and if the period for which the specified price is available is guaranteed".*

In the context of vinorelbine, no evidence has been advanced to show a transparent discounted price consistently available across the NHS for any guaranteed period and the conclusion of the Appraisal Committee is therefore inconsistent with NICE's procedures.

- At paragraphs 4.7 and 4.10, the FAD documents the Committee's acceptance of the proposition that, in UK practice, vinorelbine is not administered weekly, consistent with its marketing authorisation, but on days 1 and 8 of a 21 day cycle and that this meant that the costing for vinorelbine had been over-estimated in Eisai's model.

  The evidence relied upon by the Committee for this conclusion is not stated and it is unclear from the FAD whether this is intended to apply to all patients who receive vinorelbine in the NHS or a sub-set of such patients. Furthermore, in circumstances where the dose of vinorelbine administered will influence the effectiveness and toxicity associated with treatment, there is no indication that the Committee has considered:

  (a) whether a reduced dose of vinorelbine is consistent with the clinical benefits demonstrated in EMBRACE; and

  (b) whether a reduced dose of vinorelbine in some NHS patients, which is likely to be associated with reduced effectiveness, as compared with that demonstrated in clinical trials, may explain the clinical specialist's view that vinorelbine results in fewer adverse events than eribulin.

In circumstances where the costings in this appraisal are key drivers of cost effectiveness, the Committee's conclusions with respect to the costs of vinorelbine, which result in their view that the "real" ICER for eribulin is likely to be higher than that calculated, are unfair.

Remedy: Eisai's requests that the Appraisal Committee should be directed to reconsider this appraisal, in the context of the list price for vinorelbine and administration consistent with the summary of product characteristics.

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

NICE insisted on a Scope for this appraisal that required comparison of eribulin with individual TPC, rather than the pre-specified analyses. Eisai submitted analyses consistent with the Scope, however the references to these analyses at paragraphs 3.20 and 4.5 of the FAD (and preceding documents) is critical of them, while giving no

recognition to the fact that Eisai did not choose, but was required to provide such material.

Eisai believes that the approach of the Committee to these analyses and the unbalanced commentary in the text is prejudicial and unfair.

Remedy : Eisai requests that the Appraisal Committee should reconsider this appraisal recognising the directions issued to Eisai in the Scope and considering the analyses submitted by Eisai in that context.

2. Ground 2: The conclusions in the FAD are unreasonable in light of the evidence submitted

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

At paragraph 4.3 of the FAD, the Appraisal Committee relies upon a statement apparently issued by the clinical specialist, "*that the trial data indicated that eribulin is less well tolerated than capecitabine and vinorelbine and in particular is associated with peripheral neuropathy and alopecia (hair loss)...*" and states that it "*concluded that eribulin is associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile*". Eisai does not believe the statement attributed to the clinical specialist fairly represents the evidence provided by him to the Committee and the conclusions set out in the FAD do not, in any event, present a balanced and reasonable view of the evidence in relation to the risk of adverse events associated with eribulin.

The clinical specialist, Dr Mark Beresford provided advice to the Appraisal Committee at the first meeting on 23 June 2011. In relation to the relative toxicity of eribulin, Eisai understood him to say that he would generally use capecitabine or vinorelbine before eribulin in patients with advanced breast cancer because he has little experience with eribulin but is familiar with the adverse event profile of the other products. Eisai did not understand him to express the view referenced in the FAD

In any event, the data from EMBRACE make clear that serious adverse events were generally lower or comparable in the eribulin arm of the study than in patients receiving TPC. While inevitably it is difficult to compare individual adverse events between TPC and eribulin in circumstances where different TPCs are likely to have different adverse event profiles, the data indicate that eribulin was associated with fewer fatal adverse events and fewer discontinuations and dose interruptions due to adverse events than TPC:

- Deaths due to serious adverse events were lower in the eribulin arm than TPC (4.0% versus 7.7%);

- Discontinuations due to adverse events were lower in the eribulin arm than in TPC (13.3% versus 15.4%);

- Dose interruptions were lower in the eribulin arm than in TPC (5.0% versus 10.1%).

- The median dose intensity was 91% of that predicted in the eribulin arm of the trial, demonstrating a well-tolerated profile.

Furthermore, in view of the superior efficacy of eribulin, patients in EMBRACE continued on treatment with eribulin longer than they did on TPC (eribulin median: 118 days, chemotherapy median: 64 days and hormonal agents median: 30 days). In circumstances where patients received treatment with eribulin for a longer period, there was greater opportunity for adverse events to be experienced than patients who received TPC. In the context of the results referenced above, this further supports the favourable toxicity profile of eribulin relative to TPC.

In summary therefore:

a) It is not reasonable to conclude, based on the evidence of the clinical specialist or data from EMBRACE, that eribulin is less well tolerated than capecitabine and vinorelbine;

b) There is no proper basis for placing more weight on the incidence of alopecia and peripheral neuropathy and disregarding other more serious effects when concluding that eribulin is less well tolerated than other products;

c) While caution should be exercised in comparing data obtained from different trials, the product information for capecitabine and vinorelbine provides support for a conclusion that these products are not better tolerated than eribulin;

d) The conclusions of the Committee are inconsistent with and do not appear to have taken into account the views of patient and professional groups who described side effects associated with eribulin as "acceptable" and "likely to be manageable for patients in this setting".

Remedy: Eisai requests that the Appraisal Committee is directed to reconsider its conclusions with respect to the relative adverse event profile of eribulin in the context of the trial data from EMBRACE and the views of the patient and professional bodies.

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

The protocol for the EMBRACE trial provided that data from Region 1 would be considered in a separate analysis, in circumstances where regional differences may play an important role in influencing patient outcomes. Region 1 of EMBRACE (the EU, North America and Australia) was identified as being most likely to reflect the UK and

the UK population and therefore the most relevant to be considered by NICE for the purposes of preparing guidance on use of eribulin for the NHS in England and Wales.

However, at paragraph 4.4 of the FAD the Appraisal Committee expressed its view that it was more appropriate to base guidance on the ITT population from EMBRACE rather than the data generated by patients in Region 1. The reasons given by the Committee were: (a) the differences in survival between Region 1 and the overall ITT population were evident only for the comparator, which the Committee suggested, could be due to the small number of patients in Region 1 ; (b) patients in Region 1 did not differ in terms of overall prognosis from the remainder of the trial population; (c) the advice of the clinical specialist that UK practice and the management of advanced breast cancer differ considerably from some areas of Region 1; and (d) the Committee's view that "*the trial should be evaluated as a whole as this was how the study had been designed and powered*".

However the Committee's reasons are not valid.

(i) Points (a) and (b) are consistent with the fact that standard treatment for the patient population under consideration (i.e. TPC) is different in Region 1 and in Regions 2 and 3. Accordingly the comparator treatments from Regions 2 and 3 do not reflect NHS practice, supporting Eisai's position that guidance for the NHS should be based on the Region 1 analysis. There is no indication in the documentation available to Eisai, that the Committee even considered this explanation and no reasons why if, it was considered, the Committee rejected it. In circumstances where the choice of comparator is a fundamental part of the appraisal, it is clearly essential that guidance in England and Wales is based on the comparators that are likely to be used within the NHS setting.

(ii) Also in response to Points (a) and (b), the patients from Regions 2 and 3 of EMBRACE had received less intensive treatment than patients in Region 1, which would be likely to enhance response to TPC in a way which would not reflect the population of NHS patients with locally advanced or metastatic breast cancer at this stage in the treatment pathway. Again, this fact was not recognised or taken into account by the Appraisal Committee in concluding that it was appropriate to base guidance on the ITT population.

(iii) Eisai does not agree with the statement relied upon at Point (c) and would request clarification of the ways in which the Committee believes the treatment of patients with advanced breast cancer in parts of Region 1 differs from treatment of similar patients in the NHS. Furthermore, Point (c) has no relevance in the context of the subgroup proposed by Eisai and considered by the Appraisal Committee at its second meeting (i.e. patients who have been pre-treated with capecitabine).

(iv) Finally, the Committee's conclusion at (d) misunderstands the reasons for the trial design of EMBRACE. In order to recruit as many patients as possible in the trial for the purposes of obtaining reliable efficacy data, Eisai established trial centres in a range of countries grouped into three regions. However, recognising that there were likely to be differences in patients and/or treatment strategies in different regions, separate analysis of the data from the three regions was pre-specified. The purpose for these pre-specified analyses was to provide reliable data on the magnitude of benefit associated with eribulin therapy comparable to TPC in the relevant patient populations under consideration. The analyses of the trial data by reference to the three regions was therefore a fundamental part of the trial design which was intended to provide an appropriate population for appraisal by NICE. NICE's rejection of Region 1 is therefore inconsistent with the trial design.

In conclusion, NICE's role is to assess clinical effectiveness in the context of NHS treatment, which includes assessing the magnitude of benefit associated with eribulin compared with current standard treatment in the UK. The most appropriate population for such a comparison is provided by the data from Region 1 and the Appraisal Committee's rejection of this analysis is unreasonable.

Remedy: Eisai requests that the Appraisal Committee is directed to reconsider this appraisal using the data from region 1 of EMBRACE as the base case in view of its greater applicability to the situation of NHS patients.

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

In its Addendum Report, the ERG refers to the Kaplan Meier plots for the subgroup of patients submitted by Eisai in response to the ACD (i.e. patients who had been pre-treated with capecitabine), conclude that the survival of patients receiving vinorelbine and eribulin may converge after 2 years (i.e. that most of the benefit associated with eribulin treatment is experienced by patients with a shorter life expectancy at base-line and that patients with a longer life expectancy (closer to 2 years) at base line will derive little or no benefit from treatment). This methodology was accepted by the Appraisal Committee at paragraphs 4.12 -4.14 of the FAD. According to the DSU (page 44) in situations of incomplete survival data analysis should use visual inspection, external and clinical validity, AIC and BIC criteria and not simply rely on the log cumulative hazard plots to determine convergence. Furthermore, it is stated that parametric models should be used, rather than restricted means approaches, unless data is almost entirely complete (page 39).

Eisai provided two different modelling approaches to the estimation of overall survival in the population of patients pre-treated with capecitabine: the LRiG Method (which was the method adopted by the Appraisal Committee in the ACD for estimating the overall survival in the full EMBRACE population and does not rely on an assumption of

proportional hazards) and the proportional hazards method. Both of these approaches produced substantially higher overall survival than the method chosen by ERG (4.54 months using the LRiG Method with 35% parametisation; 3.99 months using the proportional hazards method). Furthermore, Eisai provided extensive sensitivity analyses around both approaches included in the submission. Yet both these approaches were dismissed by the ERG and the Appraisal Committee in favour of an alternative methodology, inconsistent with that adopted by the Committee at the ACD stage and inconsistent with the recommendations of the DSU (page 39-41) and based on a scientifically invalid finding of convergence. In addition the conclusion of convergence is inconstant with the analysis (based on the LRiG) upon which the final decision was made that the ICER lies at £68 800 per QALY

In summary, the reliance by the Appraisal Committee, at paragraph 4.12 of the FAD, on the approach suggested by the ERG for the estimation of overall survival is inconsistent with the methodology already approved by the Committee for the same data and with the approach recommended in the DSU's Report commissioned by NICE. This lack of consistency is arbitrary and therefore unreasonable.

Remedy: Eisai requests that the Appraisal Committee is directed to reconsider the approach to the estimation of overall survival associated with eribulin therapy in patients who had previously received treatment with capecitabine and to take this into account when applying the end of life criteria to eribulin.

REQUEST FOR ORAL HEARING

Eisai requests an oral hearing for the determination of this appeal.