NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane [ID603]

Dear [redacted]

The Evidence Review Group, the School of Health & Related Research Sheffield (ScHARR) - University of Sheffield, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 10th of December 2013 by Roche Products. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 28th January 2014. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]. Any procedural questions should be addressed to [redacted] in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on search strategies

A1. **Priority question:** Please explain why the indirect and mixed treatment comparison search of The Cochrane library was limited to one year only (2011-2012)?

A2. The different search strategies vary in terms of the number of concepts, the number of key words and subject headings used to express those concepts, and the choice of terms such as those for the intervention. Given the limited search terms used, the clinical evidence and the cost-effectiveness searches may have missed relevant studies. Please comment on the extent to which your search results were inclusive of all relevant studies.

A3. There is variation in how an individual search was applied in different databases; for example, the clinical evidence search in Medline and The Cochrane Library. Please explain the reasons for this?

A4. In the quality-of-life and cost-effectiveness searches, please explain why subject headings were not used, and why was EconLit not searched?

A5. Please explain why you did not search trials registers, for example via the Current Controlled Trials website or a comprehensive database such as the Science Citation Index Expanded and Conference Proceedings Citation Index?

Section B: Clarification on clinical effectiveness data

B1. The submission states in section 6.3.6, page 75, that 'When disease progression occurred after two or more consecutive missed tumour assessments, these events were not counted; rather, the patient was censored at the patient's last tumour assessment prior to the missing assessments.' Please present the number of events that were not counted in each treatment arm, and clarify why an interval censoring method of analysis was not considered?

B2. Please clarify the reasons why 585 screened patients were considered ineligible for inclusion in the EMILIA trial prior to randomisation (Page 81, Figure 4).

Page 142 of the submission states that the safety of trastuzumab emtansine was evaluated based on data from 884 patients. Table 23 on page 143 reports adverse reactions from 882 patients. Please clarify whether the pooled safety analysis contained data from 882 or 884 patients.

B3. Please clarify why adverse event data from JO22997 were not included in the pooled safety analysis (section 6.9.3).

B4. Please provide a complete reference for Martin (2011) (Page 114 and Table 19).

B5. Please clarify which definition of visceral disease (Page 20) was used in the PFS subgroup analysis of the TH3RESA trial (Page 21, and Page 101, Figure 14).

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B6. Please clarify whether the first two paragraphs on Page 55 (section 6.3.2) refer only to EMILIA, or to both EMILIA and TH3RESA. If they refer only to EMILIA, please provide the frequency of tumour assessments for TH3RESA.

Section C: Clarification on the indirect and mixed treatment comparisons

C1. **Priority question:** The submission states in section 6.7.5, page 122, that '… given where these treatments sit in relation to trastuzumab emtansine (T-DM1) they would not inform the comparisons of interest (see section **Error! Reference source not found.**) and hence would not change the results detailed in section **Error! Reference source not found.**'. However, trastuzumab plus vinorelbine is one of the comparators for trastuzumab emtansine, and a comparison with trastuzumab plus vinorelbine is possible only if the TH3RESA trial is included. Please clarify why the network described in Figure 18, which includes trastuzumab plus vinorelbine, was not used for this comparator or rerun the analysis including trastuzumab plus vinorelbine as a comparator.

C2. **Priority question:** From a Bayesian perspective, using a fixed-effect analysis is not justifiable when there is insufficient sample data (i.e. studies) to estimate the parameters. Ideally, the analysis should incorporate genuine prior beliefs about the parameters. In the absence of a formal elicitation method, a suitable prior distribution representing reasonable prior beliefs should be used. A prior distribution suggested in the Technical Supports Documents by NICE's Decision Support Unit is a HN(0, 0.322) distribution. Predictive distributions of a randomly chosen study would have wider confidence intervals reflecting heterogeneity between studies. Please rerun the mixed treatment comparison using a random-effect analysis and use the results of this analysis (joint posterior predictive distribution for a new study) within the economic model.

C3. The assessment of proportional hazards in the submission is based on observed data only. Is there any reason *a priori* to believe that the treatment effect is constant over the lifetime of patients during both the observed and unobserved follow-up periods? Please present supporting evidence where possible.

C4. Although inconsistency could not be assessed for all interventions (Section 6.7.7, page 125), in addition to the discussion on page 128 about the differences in baseline characteristics between studies, please discuss the imbalance in baseline characteristics between treatment arms and the impact that any imbalance is expected to have on treatment effects.

C5. The submission states on page 114 that "For the purpose of the current analyses we used, for the indirect comparison the one that excluded cross-over patients from the analysis (HR [95% CI]: 0.78 [0.62 – 0.97]; p=0.02)" (also page 130). However, the intention-to-treat results are used from the other trials included in the analysis, although cross-over may have occurred in those trials. If it is not possible to adjust for cross-over consistently between trials, please present the analysis using the intention-to-treat results from the T-DM1 trial instead of the results adjusted for cross-over.

Section D: Clarification on cost-effectiveness data

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D1. **Priority question:** Please provide the Excel spreadsheet referenced within the model for the PFS and OS parameters.

D2. **Priority question:** Please clarify why the Kaplan–Meier data were used directly to model PFS but not OS within the base-case analysis, and comment on the likely impact on the ICER if the same approach was used for OS and PFS. Also, please clarify why only the gamma and Weibull distributions were compared with the Munich registry data in Figure 36 when the log-logistic and log-normal distributions gave lower AICs than the Weibull. Please include the log-logistic and log-normal distributions within the figure and confirm whether the gamma distribution remains preferable.

D3. **Priority question:** Please amend the cost of trastuzumab emtansine and trastuzumab both within the economic model and within the budget impact calculations to resolve the following issues:

a. The average weight of a person is used. When wastage is included this will lead to inaccuracies in the calculation of total cost since it does not consider the variation in weight between people and the impact of this upon vial usage. For example, for individuals weighing 75kg rather than 70.1kg two 160mg vials would be required rather than one 160mg and one 100mg vial. The same limitation also applies to the calculation of the trastuzumab vials.
b. The formula used to calculate the number of 100mg and 160mg vials to be used per person according to their weight does not minimise the cost of the vials. For example, if a person's weight was 75kg rather than 70.1kg, the present formula would estimate that one 160mg vial and two 100mg vials should be used, whilst two 160mg vials would provide sufficient dosage at the lowest cost.
c. In the base case, it would be preferable to use the actual dose (including wastage) rather than the planned dose.

D4. **Priority question:** Since lapatinib plus capecitabine is neither strongly or extendedly dominated by the other interventions, it should not be removed from the incremental analysis and the derivation of the efficiency frontier. Thus, trastuzumab emtansine should be compared with lapatinib plus capecitabine rather than capecitabine within the incremental analysis. Please recalculate the ICERs (with the identification of interventions that are dominated and the inclusion of lapatinib and capecitabine).

D5. Please present the probabilistic results rather than the deterministic results for the base-case analysis, and provide 95% confidence intervals around the probabilistic ICERs.

D6. For the PFS hybrid Kaplan–Meier model, there is no justification for using a log-normal distribution to represent the tail of the survivor function other than it provides the best fit to the observed data. Please justify the use of the log-normal distribution to represent the tail of the survivor function.

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D7. The submission states on page 182 that 'clinical experts gave their opinion on the validity of the extrapolation conducted and the resource use and costing assumptions applied in the model based on their specialist knowledge of the subject'. Please clarify whether this means that in their clinical opinion the progression-free survival and overall survival predicted by the log-normal extrapolation of the Kaplan-Meier and the Gamma fit, respectively, were reasonable?

D8. Please provide figures showing the PFS and OS curves predicted by the model for each comparator.

D9. Please provide base-case results using a 15-year time horizon given that up to 3% of patients are alive at 10 years in the current analysis that uses a time horizon of 10 years.

D10. Please include other-cause mortality within the model or comment on why it was not included.

D11. Within the submission and the Model Inputs sheet of the model, age is specified as 52.7, whilst in the operationalised model age 47 was used to calculate utilities. Please clarify whether an age of 52.7 (rather than 47) should have been used to calculate utilities, and if so please present results using this value.

D12. Within the post-progression state, patients are allocated to no treatment (52%), 19 weeks of treatment (36%) or 38 weeks of treatment (12%) depending upon their line of therapy, and they stay in the state for approximately 1.5 - 2 years (depending upon treatment within the PFS state). This implies that patients remain alive but not on treatment for over a year. Please comment on the appropriateness of this assumption or increase the weekly cost to include longer term treatment within this state.

D13. Within the Model Inputs spreadsheet, cells E131 and E132 are defined as the Duration of Treatment for AEs in weeks for T-DM1 and lapatinib plus capecitabine respectively. However, the values within these cells are 18,144 and 15,377 respectively. Please justify the use of these values which feed into the calculation of the cost of adverse events per patient week in the model.

D14. Page 185 of the submission states that 'Only adverse events with over 2% incidence in either treatment arm of EMILIA were assumed to have resource use and quality of life impact'; however within the model adverse events are included only if there is over 2% incidence overall within EMILIA (i.e. pooled over both arms). In addition, the model assumes a 2% incidence of grade 3 **or** 4 adverse events rather than a 2% incidence of grade 3 **and** 4 adverse events. Please amend so that the model and submission are consistent.

D15. There are a number of assumptions around the costs and utilities associated with adverse events. Please provide a one-way sensitivity analysis around the costs and utilities associated with adverse events.

D16. Please provide values and justification for the probabilistic sensitivity analysis parameters used in addition to the type of distribution. For the probabilistic costs of adverse events, some of the lower bounds used to calculate the standard error are

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the mean multiplied by 0.8 whilst others are the mean multiplied by 0.5; please clarify the reason for this?

D17. The cost-effectiveness acceptability curve (CEAC) should detail the probability of each intervention being the most cost-effective, and therefore the individual probabilities should total 100%. Please correct the CEAC to consider all the interventions simultaneously.

D18. Please present a tornado diagram for the one-way sensitivity analyses, where the parameters are ordered (from highest to lowest) by their impact on the ICER.

D19. Please explain why vinorelbine was not included in Table 24 on page 156.