National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the School of Health and Related Research (ScHARR), The University of Sheffield to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **6th March 2014** using the below proforma comments table. Please ensure that you submit this pro-forma to NICE using NICE Docs. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The manufacturer's revised based case has been taken as Table 5 in the clarification questions. However this table shows the cost-effectiveness results using a random effects model for the MTC. The revised base case results were shown in Table 8 where a fixed effects model was used.	Table 18 and Table 21 in the ERG report should be replaced with Table 5 from the clarification questions and all subsequent ERG corrections should be applied from the new table.	Table 24 of the ERG report applies the ERG's random effects model to the manufacturer revised base case analysis. However a random effects model has already been utilised in this analysis (Table 21).	Since the base case was not clearly labelled within the clarification letter, the ERG believed the manufacturer's base case to be the random effects model as this is presented within the revised submitted Excel model. However, given the manufacturer's request, Tables 18 and 21 have been replaced within the report; this does not impact upon the ERG's final revised base case since our own random effects analysis has already been applied.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61 ERG report, it states that the manufacturer's univariate sensitivity analysis was flawed because "all comparisons should have been included within the one way sensitivity analysis because the appropriate incremental comparison may change for each analysis" (page 63).	The univariate sensitivity analysis was not flawed and so this should be removed or amended (see right).	All comparisons were included and analysed in the sensitivity analyses. However only the comparisons of T-DM1 versus capecitabine were presented since in all cases, all other comparisons remained outside the efficiency frontier. (i.e. for each univariate sensitivity analysis conducted, lapatinib plus capecitabine still had an ICER of	This is not a factual inaccuracy. As specified on page 63 of the ERG report, 'given that lapatinib in combination with capecitabine is neither dominated nor extendedly dominated by any of the comparators, it would be more appropriate to present a comparison of T-DM1 with this

		over £30,000 and all other interventions remained dominated	intervention'.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 56 the ERG have incorrectly interpreted the Lloyd utility value 'age' covariate. The ERG states that "First, within the model, an age of 47 years has been used to calculate utilities and this is not dependent upon the age of patients within the model. The manufacturer states that age 47 is from Lloyd et al.; however the mean age reported within this publication is 40 years. This mixed model analysis contains age as a variable so that this can be altered according to the patients of interest. However, the analysis by Lloyd et al. suggests that increasing age has a positive impact upon HRQoL. This contradicts other established sources based upon larger samples of the general population which suggest that HRQoL generally decreases with age. Given this, in combination with the subsequent issues below and the reasonable external validity of the utilities employed, the age	The use of an age of 47 is the correct way to calculate utilities.	The ERG interpretation of the age covariate in the Lloyd model is incorrect. This does not refer to the age of patients in the model. This covariate represents the age of the population the utilities were elicited from. When conducting this study Lloyd et al noted that the age in their sample was lower than that in the general population – they therefore explored the impact age could have on the participants' perception of the utilities associated with the health states. They found that in general the older the participants were the higher their perceived utility from the health state. The age 47 is the mean age of people in the UK and is inputted into the Lloyd model in order to show what utility values would have been had the value been elicited from a representative sample of the UK population. The above has been confirmed in personal communication between Roche and Andrew Lloyd and has been discussed in previous NICE	Within the paper by Lloyd et al. Table 1 shows that the mean age of the study sample is 40.16 and that the mean age from UK census and ONS data is 38.2. This suggests that the age in the Lloyd et al. sample was higher than that in the general population rather than lower. An age of 47 is not mentioned in this publication in any capacity and the ERG has not seen any personal communication between Roche and Andrew Lloyd regarding this. Moreover, within the paper there is an example of how to use the mixed model analysis for a 40-year old patient and this applies an age of 40 within the equation. Thus, based upon the paper by Lloyd et al. the stated text from the ERG report is correct.

variable has not been altered by the ERG within the model."		Appraisals.	

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 76 it states that "the MTC results show that the comparative effectiveness between treatment options is highly uncertain. If any of the comparators were to have equivalent overall survival impacts to T-DM1 then they would dominate T-DM1 due to the higher acquisition costs associated with T-DM1."	The comparative effectiveness between treatment options *other than T-DM1* is highly uncertain (i.e. between all treatment options except T-DM1). Consequently it is highly unlikely that any of the comparators would have equivalent overall survival impact to T-DM1.	With either a fixed effects or random effects model, T-DM1 has a very high probability of being the best treatment for OS and PFS. With a fixed effects model T-DM1 has a 98% chance of being the best treatment for reduced hazard of death and 99% chance of being the best treatment for a reduced hazard of progression (page 43) whilst with a random effects model although the probabilities are reduced they still remain high; 84% and 87% for OS and PFS respectively (page 46).	The MTC suggests that there is uncertainty around the comparative effectiveness of all treatment options; however we have removed 'highly' from this sentence within the ERG report so that it reads "The MTC results show that the comparative effectiveness between treatment options is uncertain (a 16% and 13% chance that T-DM1 is not the best treatment for reduced hazard of death and progression respectively)."

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 32 it states "There were a number of fatalities while on study treatment...."	This should be changed to "There were a number of fatalities <u>due to AEs</u> while on study treatment..."	Clarity of text.	The report has been revised as suggested.