National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results

calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

December 2010

Issue 1 Calculation error on the Calcs_Let sheet of the LRiG_executable_model_lapatinib+AI(061210)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Cells AI48:AI77 on LET sheet, which represents the average PPS years by year post treatment initiation for LET patients, is incorrectly referencing the cells W163:W192 on the Calcs_ LapLet Sheet instead of referencing the same range on the Calcs_Let sheet.	Correct the calculation on the LET worksheet of the LRiG_executable_model_lapatinib+AI(061210).	The amendment will generate a slightly increased ICER for the comparison of lapatinib plus letrozole versus letrozole. For a 20 year time horizon the estimated ICER will be £225,962 per QALY.

Issue 2 Error in Sampling the Decrement in Utility with Diarrhoea/Vomiting (D/V) for LAP+LET in the LRiG_executable_model_lapatinib+AI(061210)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model includes a calculation of the decrement in QALYs due to diarrhoea and vomiting (D/V) in LAP+LET patients. The default estimate of the decrement in QALYs appears to be calculated as the product of the estimated incidence of G3/4 D/V in the EGF30008 trial (8.21%) and the decrement in utility with D/V from the Lloyd study (0.0948). The resulting disutility is 0.0079 (see cell C82 of the parameters sheet). For the base-case, this calculation seems appropriate, although it assumes that patients are in the D/V state for an	Revise the calculation of sampling the decrement in utility for D/V with LAP+LET in the model	The mean PSA value for QALYs with LAP+LET, the mean PSA value for incremental QALYs with LAP+LET, and the ratio of the mean incremental costs to the incremental QALYs will be similar to the base case estimates.

average of one year which may be overly conservative. Given the small disutility (<.01), it doesn't materially affect the conclusions. However, for the PSA, the model incorrectly samples the decrement in QALYs with D/V based on the disutility for D/V from the Lloyd study—that is, for the PSA, the model fails to multiply the decrement in utility per person with the event (0.0948) by the proportion of patients with the event (0.0821). Accordingly, the mean decrement in QALYs from AEs in the PSA is approximately 0.0948 (This can be seen by taking the average of the values in cells Q7:Q1006 on the Rnums sheet). This (incorrect) decrement in QALYs due to D/V with LAP+LET largely offsets the gain in QALYs due to improved PFS with Lap+LET. Accordingly the mean incremental QALYs with LAP+LET in the PSA is underestimated by approximately 90% and the ratio of the mean incremental costs to the mean incremental QALYs is overestimated by a factor of 10. The resulting CEAC curves are accordingly severely biased/in error as is the scatter plot for the incremental QALYs vs. incremental costs. Also, the values reported in the second row of Table 28 of the report are also in error.		

Issue 3 Error in Inputs Used to Sampling the Proportion of Patients Progressing with LET in the LRiG_executable_model_lapatinib+AI(061210)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model adjusts PPS for LET using an adjustment factor of 0.953703704 calculated as 103/108 (see cells AK39:AI41 in Let sheet). For LAP+LET, the model uses a factor of 0.936936937 calculated as 104/111. For sampling the model uses beta distribution parameters of a=104 and b=7 for LAP+LET (a+b=111). However, for LET, the model uses beta distribution parameters of a=103 and b=3. To be consistent, the latter should use a=103 and b=5 (a+b=108). Note that this assumes that the values used to estimate the proportions are correct, although it is not clear how the 103 and 104 values were obtained from the EGF30008 trial data.	Check beta distribution parameters for sampling of the proportion of patients progressing.	Using the value of b=5 for LET would likely reduced the mean PSA QALYs for LET and increase the mean PSA incremental QALYs for LAP+LET vs. LET and reduce the ratio of the mean PSA incremental costs to the mean PSA incremental QALYs. The magnitude of this effect is likely small however.

Issue 4 Potential Bias in the Sampling of PFS in the LRiG_executable_model_lapatinib+AI(061210)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model samples the PFS probability in each 28 day cycle by multiplying the base-case probability by normal random variable with mean of 1.0 and standard deviation equal to the standard error of the estimated mean PFS up to 504 days. Because PFS cannot exceed 1.0, the sampled values are truncated at 1.0. Because the PFS values for LAP+LET are closer to 1.0, they are more affected by this truncation. A more appropriate method for sampling would be to apply sampling to the sum of the PFS values up to 504 days rather than the survival probabilities. This would eliminate the need for truncating the distribution at 1.0	Revise the method for sampling PFS to avoid the potential bias associated with the truncation of sampled values at 1.0.	The mean PSA value for QALYs for LAP+LET, the mean PSA incremental QALYs for LAP+LET vs. LET, and the ratio of mean PSA incremental costs to the mean incremental QALYs (labelled mean ICER) will be similar to the base case estimate.

Issue 5 Lack of transparency which limits the testing of the robustness and reliability of the LRiG_executable_model_lapatinib+AI(061210)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In general there is little information on the model inputs and results and this limits transparency and the testing of the model. Examples are as follows: The precise methods by which the two parameters of the exponential distributions for PFS after 504 days and for Post Progression Survival (PPS) were obtained using data from the EGF30008 trial is not in the model (or Assessment Report). The reason for using a 2-parameter exponential distribution (i.e., with the scaling factor) is also not described. It would appear that in order to account for the proportion of patients who died prior to progression, the model adjusts expected PPS by a constant factor. This factor is 0.9537 for letrozole and 0.9369 for lapatinib plus letrozole. According to the model, these adjustments are calculated as the ratio of “progress patients” to “all patients” in each group and are103 / 108 for letrozole and 104 /111 for lapatinib plus letrozole) (refer to ‘Let’ cells AL39 to AL41 and ‘LapLet’ cells AO39 to AO41 of the lapatinib AG model). The source of this data is unclear.	For future consultations additional information on the AG model should be provided to facilitate testing.	Unknown.

For patients who progress during each 28 day cycle, the model calculates the number of PPS days that are accrued in each year following treatment initiation. It is not clear why this approach was employed, as the model assumes a constant risk of death given progression, and the need for what are essentially “”tunnel states” for PPS is unclear. It is difficult to assess the methods by which the PSA values were calculated. It appears that the model allows for a “standardized” or “unstandardized” PSA. The former uses values for selected parameters drawn from the parameter sets in the ‘RNums’ sheet of the model. The “Unstandardized” PSA uses sampling from normal distributions. It is not clear which approach was employed in the Assessment Report. It is not possible to determine the source of the values in the RNums table that are the basis of the “standardized” PSA. There is a difference in the base case estimates given in the Assessment Report (£220,626 per QALY gained) and those shown in the model £215,504 per QALY gained (for the 20 year time horizon) for lapatinib plus letrozole versus letrozole. It appears that the reason for the difference between the results in the model and the Assessment Report relates to the utility values for PFS for lapatinib plus letrozole and letrozole. The Assessment Report		

states that these utilities are 0.7663 and 0.7623 for lapatinib plus letrozole and letrozole respectively. However, the model uses values of 0.779398257 and 0.774892291 respectively. The former are label as “original” in the model (see cells H79 and H80 on the Parameters sheet) whereas the latter are labeled as “revised” in the model (see cells I79 and I80 on the Parameters sheet). When the “original” values are used, the Model results match those in the Assessment Report. The source of the “revised” estimates is not provided, so it is impossible to ascertain which of the two sets of estimates is more appropriate. Also, it appears that the PSA is sampling based on the utility values used in the Assessment report not the revised values (see cells C41 and D41 on the Uncertainty sheet as well as the average values for cells G7:G1006 and H7:H10006 on the Rnums sheet). In general the model also incorrectly labels some cells as “utilities” that should be more appropriately labeled QALYs as they represent the product of utility values and life years. Improving the labeling/documentation of the model might facilitate the identification of calculation errors such as that described above.		