Health Technology Appraisal

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

GlaxoSmithKline welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) for lapatinib and trastuzumab in combination with an aromatase inhibitor (NICE 2010a).

Our comments on the ACD are structured below in response to the specific questions posed by NICE.

1. Has all of the relevant evidence been taken into account?

GlaxoSmithKline considers that the ACD does take into account the relevant evidence.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We believe that the summaries of the clinical and cost-effectiveness of lapatinib plus an aromatase inhibitor are not reasonable interpretations of the evidence. We have identified a number of issues with the economic evaluation conducted by the Assessment Group, which have a direct impact on the interpretation of the clinical and the cost-effectiveness evidence and potentially affect the most plausible ICER range quoted by the Appraisal Committee in the ACD. A summary of these issues is provided below, with specific details provided in our comments on the executable model for lapatinib (GSK pro-forma response).

2.1. Clinical Evidence

The outcomes benefit (QALYs gained) calculated in the Assessment Group economic evaluation implies a difference in effectiveness between lapatinib and trastuzumab that is not supported by the available clinical evidence in the patient population under consideration.

In assessing the likely long term survival benefit derived from clinical interventions, extrapolation of clinical trial benefits is required. The resulting projected survival estimates allow HTA bodies to make inferences of the long-term treatment effects on quality-of-life-adjusted survival. Our main concern in this particular MTA is the fact that different modelling techniques and assumptions have been applied to assess the long-term benefit of lapatinib plus letrozole relative to those used for trastuzumab plus anastrozole. It can be stated that the use of dissimilar approaches is not only likely to yield different results, but more importantly it might prevent the Appraisal Committee from making a comparable comparison when analysing the presented data.

The Assessment Group (AG) has chosen to model clinical benefit from the PFS curves using different methodologies for the EGF30008 and TAnDEM clinical trials (Johnston et

al. 2009; Kaufman et al. 2009). For the EGF 30008 trial, the method used by the AG assumes that no further benefit accrues to the patients who remain on lapatinib after 16 months, whilst for TAnDEM it is assumed that the benefit continues. The binary differentiation in methods is based on whether the Kaplan Meier curves for the intervention and comparator intersect at the tail.

The number of patients contributing to the PFS curves by 16 months for both EGF 30008 and TAnDEM is small. At 15 months the number of patients at risk is 20 for lapatinib plus letrozole, 18 for placebo plus letrozole, 17 for trastuzumab plus anastrozole and 9 for anastrozole alone (Johnston et al. 2009; Kaufman et al. 2009). The modelling methods used by the AG assume that all data points along the Kaplan Meier plots demonstrate statistically significant differences between the clinical benefit afforded by the intervention arm vs the placebo/comparator arm.

It seems clinically unintuitive to assume that one drug suspends all benefit after 16 months and the other retains a benefit, when:

a) The median PFS benefit of lapatinib plus letrozole is numerically higher and in all likelihood clinically comparable to that of trastuzumab plus anastrozole.
b) The modelling approach taken by the AG for lapatinib leads to a predicted OS curve that has a poor fit and underestimates the empirical overall survival data generated to date for lapatinib plus letrozole by approximately 44% (NICE 2010b page 170; GSK comments on the Assessment Report).

It should be noted that the overall survival (OS) data for EGF 30008 is not yet mature. At the time of the last data cut (3rd June 2008), 47% of deaths had occurred. The current OS data indicate a one month survival advantage for the patients taking lapatinib plus letrozole over those taking placebo plus letrozole (33.2 vs 32.2 months), although the result does not reach significance (HR=0.74; 95% CI, 0.5 to 1.1) and the data is influenced by lines of therapy subsequent to progression.

2.2. Cost-effectiveness Evidence

Errors in the probabilistic sensitivity analysis

Information from the lapatinib executable model provided by NICE suggests that there are errors in the calculation and a flaw in the methodology applied to the probabilistic sensitivity analysis (PSA). These have an impact on the plausible incremental cost effectiveness ratio (ICER) range quoted in the ACD for lapatinib plus letrozole.

Typically in a cost-effectiveness acceptability curve (CEAC) presentation of the PSA data, the curves for the intervention and the comparator cross at a point approximating the estimated base-case ICER value. For the comparison of lapatinib plus letrozole versus letrozole monotherapy, the Assessment Group's base-case estimate (as quoted in the model) is £215,504 per QALY gained (for a 20 year time horizon). The point at which the CEACs cross is, however, above £2,000,000 per QALY gained. While it is possible for the CEAC to cross at points above or below the base-case, a discrepancy of this magnitude is highly suggestive of an error in the PSA.

It should be noted that the estimated mean QALY for lapatinib plus letrozole from the PSA is 1.4806, compared with the base case estimate of 1.5813 QALYs. This results in

an incremental PSA QALY value of 0.01 instead of a value closer to the base case estimate of 0.12. This approximately 12-fold discrepancy in the QALY estimate results in a corresponding inconsistency in the average ICER (approximately £215,000 versus approximately £2,500,000 per QALY gained).

The source of the discrepancy between the mean PSA sampled value of the QALYs for lapatinib plus letrozole compared with the base case estimate of the QALYs for lapatinib plus letrozole is an error in sampling of the decrement in utility with diarrhoea and vomiting. As a consequence of this error is the 'mean' incremental QALYs for lapatinib plus letrozole versus letrozole in the PSA is underestimated by approximately 90% and the ratio of the mean incremental costs to the mean incremental QALYs with lapatinib plus letrozole versus letrozole (labelled as "Overall IC/IQ") is overestimated by a factor of more than 10-fold. The resulting CEAC and the scatter-plot for the incremental QALYs versus incremental costs are thus incorrect as is the data in Table 28 of the Assessment Report. Further details of this sampling error and other errors in the PSA are provided in the GSK pro-forma response document for the lapatinib model.

In addition to the issues above, it should be noted that the ratio of the average PSA costs and average PSA QALYs has been calculated instead of the average PSA ICER. There is however a fundamental mathematical difference between these two types of calculations which provide different information and produce different results. Specifically, the ratio of the average incremental costs to the average incremental QALYs weights each simulation by the incremental QALYs. Presumably, all simulations should be weighted equally, and the ratio of the average incremental cost to the average incremental QALYs may be subtly biased (depending on the correlation of the ICER with the incremental QALYs) when compared with the average of the ICERs. For the comparison of lapatinib plus letrozole versus letrozole monotherapy some of the simulations in the Assessment Group model fall into different quadrants of the cost - effectiveness plane which means that some have negative ICER values. It is therefore not appropriate to calculate an average PSA ICER for lapatinib plus letrozole. GlaxoSmithKline understand the possible rationale for the methodological approach adopted by the Assessment Group but questions the validity of using the ratio of the average PSA costs and average PSA QALYs.

Lack of consistency in the base case and the PSA estimates reported in the Assessment group report, the model and the ACD.

In the Assessment Report the PSA ICER was given as £2,895,994 per QALY gained; in the model the value appears to be £2,494,432 and in the ACD report the figure quoted is £960,800.

With regard to the base case ICER (for the 20 year time horizon) a value of £220,626 per QALY gained is given in the Assessment Report whilst in the model the estimate appears to be £215,504 per QALY gained. There is however a calculation error on the 'LET' sheet of the model which if corrected produces an ICER of £225,962. It appears that the reason for the difference between the results in the model and the Assessment Report relate to differences in the utility values used for PFS for lapatinib plus letrozole and letrozole. No explanation for this difference is provided and therefore it is difficult to ascertain which of the two sets of estimates is more appropriate. Further details of this issue are provided in the GSK pro-forma response document for the lapatinib model.

Lack of transparency in the Assessment Group modeling

The AG model has relatively little documentation of the model inputs and results which limits transparency and makes it difficult to conduct a thorough review of its robustness and reliability. For example, it is difficult to assess the methods by which the PSA values were calculated and whether the PSA values quoted in the Assessment Report are from the use of the 'standardized' or 'un-standardized' PSA approach. Further information transparency issues with the model are given in the GSK pro-forma response document for the lapatinib model..

Questionable face validity of OS data generated by AG model

The AG model does not reflect the actual OS data from the EGF30008 clinical trial. As previously reported (NICE 2010b page 170), GlaxoSmithKline estimated that the AG model underestimates the OS gain achieved with lapatinib plus letrozole versus letrozole. This underestimation is approximately 44% based on a comparison of the AG modeled data with the Kaplan-Meier curves from the EGF30008 clinical trial up to the end of the 46 month follow-up period. The reasons for the discrepancy between the AG model projections and the empirical survival distributions are uncertain.

All of the issues highlighted above call into question the robustness of the data analysis upon which NICE has based its provisional recommendation.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

GSK believe that whilst resolution of the issues described in point 2 above might not affect the provisional recommendation, the detail underlying this recommendation in the ACD does not reflect the true clinical and cost-effectiveness of lapatinib plus an aromatase inhibitor in the first line treatment of women with metastatic hormone-receptor-positive/HER2+ breast cancer, and should be reassessed and corrected.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

GlaxoSmithKline do not believe that there are any aspects of the recommendation that need particular consideration to ensure that NICE avoid unlawful discrimination.

5. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?"

GlaxoSmithKline do not believe that there are equality related issues needing special consideration which have not already been highlighted in our submission.

References

Johnston S, Pippen J Jr, Pivot X, et al., Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for post-menopausal hormone receptor–positive metastatic breast cancer. J Clin Oncol 2009; 23 (33):5538-5546.

Kaufman B, Mackey JR, Clemens MR, et al., Trastuzumab plus anastrozole versus anastrozole alone for the treatment of post-menopausal women with human epidermal growth factor receptor 2-positive, hormone receptor–positive metastatic breast cancer: Results from the randomized phase III TAnDEM Study. J Clin Oncol 2009; 27 (33):5529-37.

NICE 2010a, Appraisal consultation document. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2, November 2010.

NICE 2010b, Evaluation Report. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2, December 2010