2 June 2006

In confidence information removed
Eli Lilly and Company
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL

Dear In confidence information removed,

Single Technology Appraisal - Gemcitabine for the Treatment of Metastatic Breast Cancer

The Evidence Review Group, SHTAC has now had an opportunity to take a first look at the industry submission document and economic model submitted by Eli Lilly. In general terms they felt the document and model were well presented and clear. However there are a number of issues and queries on which we are seeking your feedback at this early stage.

The comments and queries included in this letter are divided into three sections:

- **Clinical evidence**
  These points are very important to enable us to understand the selection criteria for studies which were included in the clinical evidence section and subsequently in the cost effectiveness analysis, as well as their impact on the model.

- **Cost effectiveness**
  This section lists queries relating to the cost effectiveness modelling which will improve our understanding of the model inputs and outputs.

- **Textual clarifications**
  This section requests clarification in relation to the text of the submission, which may have an impact on the validity of evidence presented on clinical effectiveness and cost-effectiveness.

Both SHTAC and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Committee Meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by Monday 19 June 2006.

Yours sincerely

Meindert Boysen, *Pharmacist MScHPPF*
Associate Director – Single Technology Appraisals
Centre for Health Technology Evaluation

Section A: Clinical evidence

A1. Please provide statistical evaluations of heterogeneity for the studies from which absolute efficacy estimates were pooled (section 2.7, question 59, page 55). We specifically request that homogeneity in patients' characteristics and degree of metastatic setting is evaluated using a method such as the graphic approach and Q statistic.

A2. Please provide justification for the exclusion of a third abstract: *Moinpour, C. et al. (2004)* from Table 1 given that the inclusion/exclusion criteria for the systematic review do not specify particular outcomes. Two abstracts are cited for the JHQG study, but the submission does not include this third abstract: “Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Quality of life (QoL) and pain palliation results from the global phase III study”; Journal of Clinical Oncology 22 (14) 32(S).

A3. Please provide further details relating to the quality of life data presented in response to question 54 (pages 51 – 54). Specifically, we request:

- The absolute quality of life scores underlying the % change from baseline depicted in Figure 5.
- Further details regarding the study of pain alleviation (page 53); in particular a definition of what is meant by ‘Improved’ in Table 12 and a brief assessment of the strengths and weaknesses of this study.

A4. Please clarify the difference between ‘death’ (0 in T arm, 2 in GT arm) and ‘death from study disease’ (2 in T arm, 8 in GT arm) as presented in Table 6, Summary of Patient Disposition by Reason for Discontinuation (page 38).

A5. Please provide justification for the inclusion of ‘ovarian neoplasms’ in the search terms: pages 175-8, appendix 6.

A6. Please clarify the treatment pathway for patients diagnosed with Stage IV breast cancer and explain why these patients are ineligible for GT as indicated in the flow chart given in Appendix 1, page 155. What happens to those patients?

Section B: Cost Effectiveness

B1. Please give a brief explanation for the choice of the variables used for probabilistic sensitivity analysis (PSA) and clarify how many iterations were performed. Although the scatter plots in the submission indicate that a larger number of iterations were performed, there only appear to be ten in the Excel spreadsheet submitted. The report is clear as to the variables included in the PSA (page 129), but there is no discussion as to why those particular variables were chosen and others were

excluded (for example, assumptions over the scheduling of response rates which are included in the one-way sensitivity analysis; probability of developing toxicity, or treatment costs).

B2. Please perform a full PSA across a wider range of parameters, including as a minimum all of those which are varied in the one- and multi-way sensitivity analyses. Please state the number of iterations performed.

B3. Please clarify what is shown in the cost effectiveness acceptability curves presented on pages 137 to 139. Is each intervention being independently compared against a common comparator?

B4. Please present separate cost effectiveness acceptability curves which show the incremental cost effectiveness of each treatment option versus the comparator treatment.

B5. Please confirm whether the expected further chemotherapy cost that is applied to each cycle only applies to those who have newly entered the progressive state in the corresponding cycle.

B6. Please confirm whether the treatment discontinuation rates listed in table 35 (page 100) are pooled estimates.

B7. Please provide the additional analyses of clinical trial data relating to the table of assumptions (on page 109) about scheduling of response rates.

B8. Please provide the additional analyses of clinical trial data relating to the table of assumptions (page 110) about time to disease progression - differentiating time to disease progression for responders and non-responders.

B9. Tumour response rates:

- Please clarify why the submission states that investigator assessment will usually give higher response rates than independent assessment (page 121 of the submission) yet the proportion is higher for independent assessment in the GT arm of JHQG trial (proportion is identical for T arm).
- Please explain why the number of cases assessed is lower for the independent assessment (198 vs. 267).
- Please provide working Excel spreadsheet which describes how investigator-assessed response rates were pooled for use in the sensitivity analysis reported in table 23 (page 87).

B10. Please provide a more detailed answer to question 114 (page 133). In particular, please provide a copy of time-to-event analyses for overall survival and time-to-disease progression in trials S273 and JHQG.

B11. Please state clearly and explicitly how the health states in the model (in Excel spreadsheet) were defined. How are S4AE1, S4AE2 and S4AE3 different from SAE4? The same applies to R4AE1, R4AE2, R4AE3 and RAE4? Also, please illustrate how the transition probability, expected utility score and expected cost for each of these states were estimated?

B12. Please advise the source for the uplift to 2005/06 prices. Costs are reported as being inflated to 2006 prices using the Pay and Prices Index reported by PSSRU, however, there does not seem to be a reference that gives the Pay and Prices Index for the 2005/06 financial year - the 2005 Unit Costs of Health and Social Care (the most recent we can find) gives values for 1995/96 through 2003/04 and an estimated value for 2004/05.

Section C: Textual Clarifications

C1. Please confirm whether the figures in Table 17 (page 62) are percentages or absolute numbers.

C2. Please clarify whether the 5.72% figure cited for the Chan et al study in table 32, page 97 is a typing error. Shouldn't a corresponding frequency be given or was the data "Not Registered'?

C3 Please provide a full answer for question 92. The answer in the submission refers to question 87 but this does not seem to contain sufficient detail on survival.

C4. Please provide the reference for the study by O'Shaughnessy et al. 2004 (page 116).There is no reference provided in the submission.

C5. Please clarify whether the reference to Lloyd 2005 is correct (page 124) or whether it should read 2006. No 2005 paper is given in the reference list for the document.

C6. Please clarify whether the figure inserted on page 64 has been inserted in error. The figure doesn't seem to reflect the discussion in the text.

C7. Please provide a key to the superscripts which appear in Table 43 (page 133) as no key was provided in the submission.