www.lilly.co.uk

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL

Tel: +44 (0) 1256 315000

HTA Strategy

Medical and Product Information: +44 (0) 1256 315999

19th June 2006

Dr Meindert Boysen
Associate Director – Single Technology Appraisals
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Dr. Boysen

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

Thank you for forwarding the questions/queries from the Evidence Review Group at SHTAC based on the above appraisal.

We have responded to your questions by following the format of your letter. Therefore our response is also split into three sections:

- **Clinical evidence**
- **Cost effectiveness**
- **Textual clarifications**

Please be advised that our response contains confidential information which has been removed and marked confidential information removed.

We would like to include a copyright disclaimer on the submission prior to its publication on the NICE website; therefore we will forward a new copy of the submission with this disclaimer included. The submission will be exactly the same as that sent on 17 May 2006, with the exception of this disclaimer.

We trust that this is satisfactory.

Yours sincerely

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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.

Information extracted from the phase III RCTs on patient characteristics was used to assess the homogeneity of patients in a non-quantitative manner. This was due to differences in the reporting of key characteristics such as the site(s) of metastases and the number of metastatic sites. Tables A1-A3 (shown in Appendix 1 below) illustrates the variation between studies in how these data were presented. There was not one single variable upon which a formal (quantitative) comparison of homogeneity could be reliably performed, with the exception of data on patients' age (which are of limited value in terms of demonstrating the comparability of patient populations in this context)

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).

The abstract by Moinpour (2004) was not retrieved in the systematic search conducted by Lilly, although there was no reason for this considering the inclusion/exclusion criteria.

The quality of life and pain palliation data presented in the submission and in this abstract were based on JHQG clinical trial, therefore the information is not expected to differ. Clinical outcome data were consistent with data presented by Albain K et al, Proc ASCO 2004.

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.**

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- **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.**

Health outcomes were measured through both objective and subjective endpoints. The corroboration of endpoints would increase the confidence in the clinical significance of the results. Subjective endpoints were obtained from patients by completion of the Brief Pain Inventory (BPI) and Rotterdam Symptom Checklist (RSCL). Objective measures, prospectively determined as important in patients, included class of pain medications consumed (analgesic level).

One hundred forty-one patients on the GT Arm and 150 patients on the T Arm completed at least one BPI. A total of 231 patients did not complete the BPI because of the lack of validated translations, and 7 patients did not complete the BPI for other reasons. For investigational sites with validated translations, on-study compliance rates (defined as the number of questionnaires completed divided by the total number of expected questionnaires based on cycles administered) were 84.9% for the GT Arm and 84.6% for the T Arm.

For patients who completed the BPI, analyses were performed on both an ITT population and a subset population that included only those patients who were symptomatic at baseline. The symptomatic subset included all patients with a baseline analgesic level ≥ 1 (that is, use of any analgesics). Eighty-one patients on the GT Arm and 71 patients on the T Arm were considered symptomatic at baseline. Analgesic level was well balanced between the treatment arms for all randomized and symptomatic patients. The distribution of analgesic level for the patients with BPI data was similar to that of all randomized patients; this suggests that results from patients with BPI data could be extrapolated to the entire study population.

The analyses of the BPI data included the analysis of a single question, referred to as "worst pain," and the analysis of the mean of seven questions that addressed the impact of pain on various aspects of life, referred to as "mean BPI interference items". Scores for the BPI are reported on a scale of 0 to 10, with 0 representing no pain or the pain does not interfere with daily living.

When the data were summarized at the individual patient level, more patients on the GT Arm reported at least two consecutive improvements from baseline in analgesic level during the course of therapy. These improvements were noted primarily in patients with baseline analgesic levels of 1 and 2. Table 12 in the submission summarizes the results of improved analgesic level.

'Improvement' was defined as a score better than baseline (i.e., lower or decreased) over >=2 consecutive cycles.

Strengths and weaknesses of pain analyses (BPI and analgesic level)

Strengths

- BPI is a reliable and valid tool for pain assessment; only used translations that had been validated

- objective (analgesic level) and subjective assessment
- analyses and subgroup of symptomatic patients were defined in a priori in protocol
- on-study compliance was relatively good (85%)
- subgroups appear to be balanced (although baseline pain or analgesic level were not part of stratification, other factors such as KPS and visceral/non visceral disease may have helped control for any imbalance)
- improvement in analgesic level needed to be sustained (much like tumour response criteria)

Weaknesses

- only subgroup of patients participated in BPI analysis due to lack of validated translations
- small proportion of patients with pain at baseline and even those were managed with weak analgesics (NSAIDs); however, this is consistent with the performance status of these patients; little opportunity for numerical or statistical improvement
- no quantitative data on analgesic use (analgesic diary which may note changes in analgesic consumption within an analgesic level)
- no long-term data are available

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).

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

'Ovarian neoplasms' in the search strategy because we used a pre-existing strategy suggested by NICE: http://www.nice.org.uk/pdf/taxanesreviewhtareport.pdf (pages 63 & 64).

This search term is unlikely to have resulted in exclusion of relevant paper but may have only contributed to volume rather than compromise the accuracy of the search.

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?

Patients who are diagnosed with metastatic disease and who have not received prior chemotherapy would not be eligible to receive GT. This is in line with the gemcitabine licence for breast cancer which states that patients are required to have received one anthracycline-based chemotherapy regimen in the adjuvant/neoadjuvant setting. A non-anthracycline-based regimen in the adjuvant/neoadjuvant setting is required if use of an anthracycline was clinically contraindicated.

Almost all the patients in JHQG received prior chemotherapy (GT =100%, T = 99.2%) in the adjuvant/neo-adjuvant setting.

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).

The PSA variables were selected as the key model parameters, deemed most likely to have impact on the cost effectiveness results, for which we had credible ranges pre-described (or calculable) to represent the level of uncertainty in the mean or median parameter values.

These variables covered

- utility weights
- tumour response rates
- time to progression (All)
- time to progression (responders)
- overall survival duration
- AE discontinuation rate

All the remaining sensitivity one-way analyses were based on scenarios where we considered the impact on the results from setting the model to a range of alternative assumptions or treatment scenarios – for example using a different assumption on body surface area (impacting on treatment costs).

These one-way analyses are therefore intended to demonstrate the scale of shift in results that alternative assumptions would have – in fact these had little impact overall and confirmed that the main area of variability lay in the key PSA parameters.

The standard PSA results and CEAC curves were based on a data set of incremental costs and benefits based on 5000 iterations of the model (the model version provided was set at 10 iterations purely to limit the file size for electronic transfer – and no analyses were based on this)

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.

A sub-set of the one way analyses did vary specific parameters across a value range

- Use of wig for alopecia sufferers (50-100%)
- Non drug unit cost variation (85% to 115%)
- Duration of hospitalisation for treatment of serious AEs (2 to 14 days)

We have therefore run a set of PSA analyses which also include these variables – based on the min max range assumed and also adopting a uniform distribution across the range (maximising the variability).

Confidential CD includes updated PSA analyses.

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?

The CEA curves on pages 137 and 139 show the probability of reaching cost effectiveness for a range of cost effectiveness threshold values (cost per QALY and cost per life year values).

The treatments have been independently compared against a common comparator based on monotherapy docetaxel 100mg/m^2 (therefore docetaxel does not have a line on the charts)

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

We have re-run and provided combined and separate CEACs for the treatments – based on the new PSA including the 3 additional parameters identified above in B2.

Please refer to accompanying CD for separate CEAC curves for each treatment for QALY and LY - as well as the multiple CEAC charts we originally provided.

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.

Yes, the further chemotherapy cost is only applied as a one off total cost (based on an expected number of cycles of 3rd line treatment) applied at the point of progression.

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

Yes, the discontinuation rates are treated in the same way as the efficacy variables and have been pooled for treatments that have multiple trial sources.

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

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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.

Appendix 3 confidential information removed

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).**

  In general one might anticipate investigator-assessed tumour response may be subject to a degree of observer bias favouring the new treatment, despite using objective criteria. With independent assessment of imaging this is eliminated and a more structured, accurate assessment of the extent of disease at all time points in the study is obtained. We cannot explain the reason for the higher proportion of response in the independently assessed tumour response in JHQG other than as a reflection of the subjectivity of investigator assessment.

- **Please explain why the number of cases assessed is lower for the independent assessment (198 vs. 267).**

  For the peer (independent) review of lesion data, patients with only lesions assessed by physical exam (with or without bone lesions) were NOT sent for peer review. Therefore, the number of patients with best response for investigator assessed and peer (independent) reviewed are different, i.e., independent review is lower than investigator review.

- **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).**

  The use of investigator response rates and the pooling of response data is contain in the Excel model within the Response section of the Default Data sheet – in row 289 (can also be accessed using the default button on the Input Efficacy sheet).

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.

Transition probabilities for tumour response and AE events were obtained from detailed analysis of the clinical trials available to us, using the tables of data by cycle from JHQG and S273. The distribution of responders and febrile neutropenia events was 'front-loaded' in the first few cycles and the transition probabilities reflect this (e.g. see tables provided in answer to question B7). Transition probabilities for TTDP and OS were assumed to have a constant risk following the exponential distribution of the 'survival' curves provided in the study report.

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?

In the model the stable and responsive patients could also be experiencing one of a number of adverse events as represented in the model.

To apply the costs and disutilities of these events the individual AEs were clustered into like groups

These AE groups are defined below

Life Threatening AE (Group AE 1)
Febrile neutropenia - cycle 1
Febrile neutropenia - cycle 2
Febrile neutropenia - cycle 3
Febrile neutropenia - cycle 4+

Hospitalised AE (Group AE2)
Diarrhoea / Vomiting
Stomatitis

Non-Hospitalised AE (Group AE3)
Fatigue including asthenia
Hand-foot syndrome
Neutropenia

Chronic Long Term (Group AE4)
Alopecia (Hair loss)
Neuropathy

The costs and utility estimates for each AE group were based on the specific % and distribution of AEs for each specific 2nd line chemo treatment option – this generated a weighted average cost and utility for AE1-4

This process was repeated separately for Stable and Responsive health states.

Details of this pooling process can be found in the model on the Data Store sheet in rows 100-145.

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.

We used an estimated inflation factor for 2005/2006 based on previous years ratios from the PPI (rather than leave the cost data in 2004-5 prices).

Year	**Pay and Prices Index (1987/8=100)**	**% Increase**
2003/04	225.6	
2004/05 (E)	234.2	1.038121
2005/06 (Estimated in the Model)	(234.2*1.038121) = 243.1	

Section C: Textual Clarifications

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

The figures in Table 17 are percentages.

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'

The 5.72% figure is a typing error as it should be blank - what the model does do is assume the same level of neuropathy for GD as seen with GT – which is the 5.72% figure (as no other data were available). Please note that a similar error occurs in Table 30 but this did not make a difference in the model.

We have also noted an error on table 36. Instead of the costs representing a 55% reduction, the costs represent a 45% reduction. A revised copy of table 36 is provided below. The costs are correct in the model so the mistake does not impact the results.

Table 36: Unit Costs of Chemotherapy Treatments

Treatment	Administration	Pack Name	Pack Size	Pack Cost	Off-patent price
Gemcitabine	Injection, powder for reconstitution		1000	£162.76	
Gemcitabine	Injection, powder for reconstitution		200	£32.55	
Paclitaxel	Concentrate for intravenous infusion	6mg/mL	30	£116.05	£52.22
Paclitaxel	Concentrate for intravenous infusion	6mg/mL	100	£347.82	£156.52
Paclitaxel	Concentrate for intravenous infusion	6mg/mL	150	£521.73	£234.78
Paclitaxel	Concentrate for intravenous infusion	6mg/mL	300	£1043.46	£469.56
Docetaxel	Concentrate for intravenous infusion	40mg/mL	20	£162.75	
Docetaxel	Concentrate for intravenous infusion	40mg/mL	80	£534.75	
Capecitabine	Tablets, f/c, peach		150	£0.74 (per tablet)	
Capecitabine	Tablets, f/c, peach		500	£2.46 (per tablet)	

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.

Overall survival is defined in 9 of the 14 RCTs (Albain et al., 2004; Chan et al., 1999; 2005; Jones et al., 2005; Nabholtz et al., 1996, 1999; Icli et al., 2005; Winer et al., 2004; Sledge et al., 2003).

Six of these studies adopted the same definitions, with the exception of Icli et al., (2005).

Here is the most commonly used definition:

- Overall survival was calculated from the date of randomisation to the date of death from any cause

Winer et al., (2004) and Sledge et al., (2003) defined survival as:

- 'calculated as the time from study entry to date last known alive or to date of death'.

Icli et al., (2005) on the other hand defined overall survival as:

- The time interval between the first day of treatment and date of death.

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

This is an error; the reference is O'Shaughnessy et al. 2003, which has been provided.

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.

The reference should read Lloyd 2006. The manuscript has been submitted to the British Journal of Cancer.

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.

The figure has been inserted in error. The correct figure is provided below:

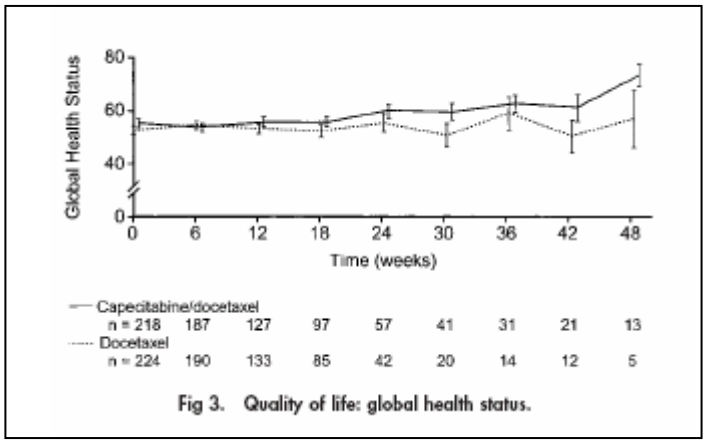

Fig 3. Quality of life: global health status.

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

The key for Table 43 is as follows:

[1] Based on the difference between Overall Survival and Time to Progression
[2] Assumes that the majority of the treatment response is achieved early in the treatment and the remaining response is achieved at a constant rate per cycle over the remaining treatment cycles
[3] Calculated in the model as the patients who remain in the stable state after applying per cycle probabilities of progression, response or death
[4] Based on FN per cycle data from; JHQG trial (for GT), S273 trial (for GD), assumed as T (for D), JHQG trial (for T), S273 trial (for DC)
[5] Based on AE rates taken from the pooled trial data for each treatment option
[6] Transition rates for response, probability and death have been derived by assuming an exponential curve form for the time to event – i.e. an assumed constant risk per cycle for treatment response, progression and death (for response an initial higher response rate was included for the first cycle of response)
[7] Based on the pooled discontinuation rates for AE or patient request from the identified trial

Appendix 1. Supporting data for Question A1.

Table A1: Sites of metastases

Study	Brain	Peritoneum	Visceral metastases	Lymph nodes	Lung metastases	Other	Pleura	Bone	Skin	Liver metastases	Non-visceral only metastases	Soft tissue
Albain et al., (2004)			Y		Y	Y				Y	Y	
Chan et al., (2005)					Y					Y	Y	
Bonneterre et al., (2002)					Y	Y	Y	Y	Y	Y		
O'Shaughnessy et al., (2002)				Y	Y			Y	Y	Y		
Sjostrom et al., (1999)			Y					Y		Y		Y
Jones et al., (2005)												
Nabholtz et al., (1999)			Y					Y		Y		Y
Chan et al., (1999)			Y					Y		Y		Y
Extra et al., (2005)												
Mouridsen et al., (2002)			Y					Y				Y
Icli et al., (2005)	Y	Y		Y	Y			Y	Y	Y		
Gradishar et al., (2005)				Y	Y			Y		Y		Y
Winer et al., (2004)			Y					Y				Y
Sledge et al., (2003)			Y									Y

Table A2: Number of metastatic sites

Study	1	2	2-3	3	3-4	>3	4	>5	5-6	7-8
Albain et al (2004)	Y	Y		Y			Y	Y		
Chan et al (2005)	Y	Y				Y				
Bonneterre et al (2002)	Y	Y		Y		Y				
O'Shaughnessy et al., (2002)	Y	Y				Y				
Sjostrom et al., (1999)	Y	Y				Y				
Jones et al., (2005)		Y								
Nabholtz et al., (1999)	Y	Y				Y				
Chan et al., (1999)	Y	Y				Y				
Extra et al., (2005)										
Mouridsen et al., (2002)						Y				
Icli et al., (2005)	Y	Y				Y				
Gradishar et al., (2005)	Y		Y			Y				
Winer et al., (2004)	Y	Y			Y				Y	Y
Sledge et al., (2003)	Y	Y				Y				

Table A3. Performance status

Study	KPS≥90	KPS≥80	KPS, n (%) 70 = 80 = 90 = 100 =	WHO Performance Status 0 = 1 = 2 =	Median KPS, %	Median KPS, (Value given)	ECOG Median	ECOG Status 0 = 1 = 2-3 =	Day 1 PS 0 = 1 = 2 = 3 = Unknown =
Albain et al (2004)	Y	Y							
Chan et al (2005)			Y						
Bonneterre et al (2002)				Y					
O'Shaughnessy et al., (2002)					Y				
Sjostrom et al., (1999)				Y					
Jones et al., (2005)						Y			
Nabholtz et al., (1999)						Y			
Chan et al., (1999)						Y			
Extra et al., (2005)									
Mouridsen et al., (2002)							Y		
Icli et al., (2005)				Y					
Gradishar et al., (2005)								Y	
Winer et al., (2004)									
Sledge et al., (2003)									Y

Appendix 2

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Appendix 3

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