27th August 2009

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Dear Mr [redacted],

Single Technology Appraisal – Pemetrexed for the maintenance treatment of non small cell lung cancer

The Evidence Review Group (Liverpool Reviews & Implementation Group) and the technical team at NICE have now had an opportunity to take a look at submission received on the 10th August 2009 by Eli Lilly and Company. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to respond to the points raised 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 **17:00, Thursday 10 September 2009**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Panagiota Vrouchou/Raphael Yugi – Technical Leads (Panagiota.Vrouchou @nice.org.uk, Raphael.Yugi@nice.org.uk)
Any procedural questions should be addressed to Laura Malone – Project Manager (Laura.Malone@nice.org.uk) in the first instance.

Yours sincerely

pp Meindert Boysen
Programme Director – Appraisals
Centre for Health Technology Evaluation

Attached – Confidentiality checklist

Section A: General:

A1 Adverse events

a) Please provide the file“DOF_JMEN_grade3/4AEs_ITT_non-squamous”. Table 12 (in the manufacturer submission,pp. 52) references this file but the file is missing from the documentation provided.

Section B: Clarifications of the effectiveness data

B1 Subgroups

a) Please provide overall survival (OS) and progression free survival (PFS) hazard rations together with confidence intervals and the actual OS and PFS figures for the licensed non-squamous population for each of the following subgroups by trial arm:

- Disease stage (presenting outcomes for stage IIIb separately from stage IV)
- Response status prior to maintenance therapy (presenting outcomes for patients assessed as complete response at the start of maintenance, separately from partial response patients and again separately for stable disease patients)
- First-line treatment (presenting outcomes according to the first line regimen – so gemcitabine/cisplatin, docetaxel/cisplatin, paclitaxel/cisplatin gemcitabine/carboplatin, docetaxel/carboplatin and paclitaxel/carboplatin patients analysed separately)
- First-platinum treatment (cisplatin separately from carboplatin)
- ECOG performance status (PS0 separately from PS1)

B2 Second-line therapy

a) Please provide a breakdown of second-line therapy (for the licensed non-squamous population) by trial arm, explaining the reasons for second-line therapy (whether progression or adverse events or other reasons).

b) Please provide further clarification and justification of the 18.5% cross over reported in the submission (did cross-over always occur after unblinding, and did it always count as second line treatment?).

c) Please provide a breakdown of second-line therapy by stage of disease for the licensed non-squamous population.

d) Please also provide the mean and maximum number of second line chemotherapy cycles for each trial arm for the licensed non-squamous population.

B3 Analysis by geographic region

a) Please provide the results of any analyses undertaken by geographical region or centre for the licensed non-squamous population.

B4 Reasons for discontinuation

a) Please provide information on reasons for discontinuation for the licensed non-squamous population for each trial arm

Section C: Clarifications of the economic data

C1 Individual patient data

a) To allow for a probabilistic sensitivity analysis to be undertaken, please provide a limited anonymised extract of the individual patient data from the JMEN trial for each non-squamous patient as follows:

- unique anonymised patient identifier
- trial arm (pemetrexed or placebo)
- days from randomisation to disease progression/withdrawal or censoring re-progression/withdrawal
- censoring for progression/withdrawal (yes/no)
- days from randomisation to death or censoring re-death
- censoring for death (yes/no)
- cycles of trial medication administered
- cycles of second-line chemotherapy administered
- type of second-line chemotherapy administered (list agent(s) or state "none")
- days from randomisation to start of second-line chemotherapy
- disease stage at baseline (IIIB/IV)
- performance status at baseline (PS0/1)
- histological sub-type (adeno/large cell/other)
- response status prior to maintenance (complete response/partial response/stable disease)

C2 Anti-emetic therapy

a) Please provide the following for the licensed non-squamous population and for each trial arm:

- medications prescribed
- duration of treatment for each episode

- number of patients given anti-emetic therapy at any time
- total number of anti-emetic treatment episodes (or the total number of patient cycles in which treatment was given)

C3 Dose reduction

a) Please provide the following for the licensed non-squamous population and for each trial arm:

- total number of planned cycles of trial medication
- total number of planned cycles where 100% of the planned dose was given
- total number of planned cycles where 75% of the planned dose was given
- total number of planned cycles where 50% of the planned dose was given
- total number of planned cycles where none of the planned dose was given (i.e. missed cycles)

C4 Hospitalisations

a) Please provide the summary information given in Table JMEN.12.10 of the Clinical Study Report (CSR_main, pp. 143) for the licensed non-squamous population.

b) Please provide further details of the hospitalisations the licensed non-squamous population as follows:

- time/cycle in which episode occurred
- length of stay
- description and HRG/DRG code for the episode
- any AEs related to the episode

C5 Adverse events

a) Please provide the number of episodes of toxicity as well as the number of patients suffering at least one episode (or the number of patient cycles involving an episode) for the licensed non-squamous population.

b) Table 12 of the Manufacturer's submission (MS, page 52) references the file "DOF_JMEN_grade3/4AEs_ITT_non-squamous" but this file is missing from the documentation provided. Please provide this table.

C6 Transfusions

a) Please provide information for the licensed non-squamous population together with the total number of each type of transfusion given (i.e where a patient receives multiple transfusions).

C7 Type of scan patients received in the trial

a) Please provide information on the proportion of patients receiving chest-x ray, MRI and CT scan for the licensed non-squamous population and for each trial arm.