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HTA Strategy

Medical and Product Information:

1st March 2007

Dr Carole Longson
Appraisal Programme Director
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
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Dear Dr Longson

Re: APPEAL BY ELI LILLY AND COMPANY LIMITED IN RELATION TO THE FINAL APPRAISAL DETERMINATION FOR PEMETREXED DISODIUM FOR THE TREATMENT OF NON-SMALL CELL LUNG CANCER

Following consideration of the Final Appraisal Determination (FAD) issued by NICE in relation to pemetrexed disodium for the treatment of non-small cell lung cancer, Eli Lilly and Company Limited (Lilly) provides formal notification of its intention to appeal. Lilly requests a hearing before NICE's Appeal Panel for the determination of this appeal.

1 Introduction

1.1 Appraisal of pemetrexed disodium: procedural history

Pemetrexed disodium (Alimta) is a multi-targeted difolate, indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. It is the subject of a marketing authorisation granted by the European Commission under the centralised procedure on 20 September 2004, following a favourable decision by the CHMP issued on 23 June 2004.

NICE initially commenced an appraisal of treatments of NSCLC under its multi-technology appraisal (MTA) procedure. This was originally intended to be limited to another agent, erlotinib but, in April 2005, Lilly was advised by NICE that the appraisal was to be extended to include pemetrexed disodium. However, the combined MTA, had not commenced when the appraisal was converted to two single technology appraisals (STAs) in Spring 2006. The current appraisal is therefore focussed only on pemetrexed disodium.

It should be noted that pemetrexed disodium was one of the first products to go through the STA procedure. NICE announced the STA as a new procedure for the rapid appraisal of important new drugs and health technologies in September 2005. The draft interim guide to the new STA was produced and subject to consultation between November 2005 and February 2006. The draft, interim STA procedure included no scoping stage or definition of the "decision problem".

Following consultation, these deficiencies in the interim process were corrected and NICE's guide to the single technology appraisal process was issued in September 2006. However, the STA of pemetrexed disodium was commenced prior to publication of the final STA guide and was therefore conducted in accordance with the interim procedures.

On 29 June 2006, Lilly provided a submission of the evidence relating to pemetrexed disodium to the Institute. That submission described the remit for the appraisal as being "to assess the clinical and cost effectiveness of pemetrexed compared to current standards of care in second-line advanced non-small cell lung cancer."

The Liverpool Reviews and Implementation Group (LRiG) was commissioned by the NHS R&D HTA programme on behalf of NICE to prepare an expert review group (ERG) report. In preparing this report, LRiG had access to the evidence submitted by Lilly but not, in accordance with the interim STA procedure, to evidence submitted by other consultees or commentators to the appraisal, including patients groups and professional bodies. Following consideration of the technology and Lilly's submission, LRiG requested clarification of several issues. Lilly responded to this request, providing the information sought by LRiG on 8 August 2006. LRiG then completed its report on 1 September 2006. LRiG was then asked by NICE to prepare an additional analysis comparing pemetrexed to best supportive care. This analysis was completed on 9 October 2006.
The Appraisal Committee met for the first time to consider this appraisal on 11 October 2006. Following this meeting, an Appraisal Consultation Document (ACD) was issued in November 2006. The preliminary recommendations, provided at paragraph 1.1 of the ACD, were as follows:

> "*Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small cell lung cancer*".

Lilly submitted its comments in relation to the ACD by letter dated 4 December 2006, explaining why the preliminary conclusions were incorrect and addressing issues raised by the ERG in its reports. Comments were also provided to the Institute by other consultees, including patient groups, professional bodies and the Department of Health. These organisations expressed the view that pemetrexed disodium should be recommended for at least some patients with locally advanced or metastatic NSCLC.

The Appraisal Committee met for a second time to consider pemetrexed disodium on 11 January 2007 and, following this meeting, a Final Appraisal Determination (FAD) was issued on 8 February 2007. The guidance contained paragraph 1.1 of the FAD, reflected the preliminary recommendations present in the ACD.

1.2 Pemetrexed disodium and the treatment of patients with locally advanced or metastatic non-small cell lung cancer

Lilly assumes that members of the Appeal Panel will have varying experience of lung cancer and its treatment. A brief introduction is therefore set out below, but does not replace the more detailed information contained in Lilly's original submission to the Institute, for the purposes of this STA.

Lung cancer (particularly NSCLC) is a common malignancy with a poor prognosis. NSCLC accounts for approximately 80% of diagnosed lung cancers and about 90% of cases are caused by cigarette smoking.
The prognosis for patients with NSCLC is poor because most patients present with advanced disease: approximately 30% of patients present with locally advanced

disease and 45% with metastatic disease. The five year survival rates for these patients ranges from 15% to less than 5%.

For patients with advanced disease, chemotherapy represents the main focus of disease control and palliation. In considering appropriate chemotherapy regimens, a key factor is not only improvement in survival and objective tumour response, but also considerations of associated side effects and quality of life. The first line therapies are based on a combination of platinum and either a taxane, gemcitabine or vinorelbine. The efficacy of all these combinations are similar and, while they are effective, virtually all patients with advanced NSCLC will relapse. For patients who do relapse following first line therapy, there are only three active treatments licensed for use in the UK in the second line setting: pemetrexed, docetaxel and erlotinib.

2 Grounds of Appeal

Lilly brings this appeal under all of the three grounds permitted under NICE's appeal procedures, namely:- Ground 1 (Procedural Unfairness); Ground 2 (Perversity); and Ground 3 (Excess of Powers).

2.1 Ground One: Procedural Unfairness

2.1.1 Two of the clinical experts were unable to provide a perspective in relation to pemetrexed disodium

An important aspect of NICE's procedures is the invitation of clinical experts to provide evidence to the Appraisal Committee in relation to the experience and use of technologies under consideration within the NHS. Lilly believes that the involvement of the clinical experts is particularly important in the context of the interim STA procedure, where there was no possibility for patient bodies or professional organisations to make submissions prior to the initial consideration of the evidence by the Appraisal Committee.

NICE's Guide to the Technology Appraisal Process indicates, at paragraph 4.4.3.2, that such clinical experts are chosen "*on the basis of the extent and nature of their experience of the technology, the disease and the services provided by the NHS to patients with the condition(s) that the technology is designed to treat*". NICE's Methods of Technology Appraisal makes clear that experts are expected to provide a written submission to the Appraisal Committee, summarising their views.

During the STA of pemetrexed disodium for NSCLC, three clinical experts, Dr Mary O'Brien, Dr Elizabeth Sawicka and Professor David Ferry, were invited to provide written submissions for the Appraisal Committee, using the expert template provided. However of the three experts only one, Professor Ferry provided a proper submission considering use of pemetrexed disodium in the form required.

- Dr Sawicka made no comments in relation to use of pemetrexed disodium, stating "I have limited knowledge of pemetrexed disodium and I do not feel I am able to comment on the relative benefits of this drug compared to other available second-line chemotherapy in non-small cell lung cancer".
- Dr O'Brien completed only a small part of one of the four sections of the expert template provided by NICE and therefore was unable to address a substantial number of the issues identified by the Institute as being relevant to its consideration of pemetrexed disodium.

Therefore, while the Institute invited three clinical experts to provide perspectives on use of pemetrexed disodium, it was provided with a full submission from only one expert and had insufficient evidence available from UK clinical experience (e.g. in relation to areas of controversy such the number of treatment cycles used in UK practice) to make an informed decision on use of the product in NHS practice. One of the experts (Dr Sawicka) had limited knowledge of the technology and should not therefore, consistent with NICE's procedures, have been invited to participate. In circumstances where the Appraisal Committee properly realised the requirement to obtain a range of clinical expert opinion, the lack of such evidence in this appraisal represents a procedural flaw.

2.1.2 <u>The appraisal has lacked transparency and this has prejudiced Lilly's ability to participate in the process</u>

From its inception, NICE has accepted the requirement for transparency in its procedures, both as a matter of fairness, but also to ensure that guidance issued to the NHS is credible and may be acted upon.

This requirement for transparency necessitates firstly the disclosure to consultees of evidence relied upon by the Appraisal Committee in formulating its guidance (unless there is some exceptional reason why such evidence may not be made available) and also sufficient reasoning to enable consultees (and subsequently those seeking to apply NICE guidance) to test the decision making process and to understand the Institute's analyses, conclusions, recommendations and advice. In the absence of proper transparency, the basis for the guidance issued is unclear, consultees are prejudiced in their ability to engage with the appraisal process and clinicians seeking to implement the guidance, will be unable to assess the extent to which it may properly apply to their patients.

However, despite these requirements, the appraisal of pemetrexed disodium for the treatment of NSCLC lacks transparency in a number of important respects and this has hampered Lilly's ability to understand the basis for the conclusions reached and to participate fully in the appraisal process.

2.1.2.1 <u>The Appraisal Committee has provided no explanation for its conclusion that changes to the mean BSA used for the economic calculation would not substantially change the ICER</u>

In the economic model submitted by Lilly to the Institute, the mean body surface area (BSA) for patients receiving pemetrexed disodium was based upon the ACTION pan European observational study of patients with NSCLC[1] which included 196 patients from the UK. In this study, the mean BSA of patients diagnosed with NSCLC (i.e. commencing first line treatment for their condition) was $1.8m^2$. Following discussion with experts, for the purposes of its economic modelling, Lilly reduced this figure to $1.7m^2$ in recognition of the fact that the majority of NSCLC patients will lose weight during the period following initial diagnosis and before there is any requirement for second-line treatment with pemetrexed disodium,

The ERG however disagreed with Lilly's approach based its calculations on an Australian study of chemotherapy patients[2] which provided a mean BSA of $1.83m^2$

[1] Bischoff et al. Palliative chemotherapy of non-small cell lung cancer (NSCLC). Baseline data analysis of the ACTOPN observational study in 5 European countries. Presented at ASCO, May 2005. Abstract No 7216.

[2] Holmes et al. A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer. Pharmacoeconomics 2004;22(9): 581-589

for patients receiving second line chemotherapy for a variety of malignancies. As explained in its response to the ACD dated 4 December 2006, Lilly believes the approach followed by the ERG is inappropriate for the following reasons:

- NICE's procedures provide that the focus of the evidence considered by the Appraisal Committee should be the UK and that where data from outside the UK is relied upon, this constitutes a deficiency in the evidence base (NICE's Guide to the Methods of Technology Appraisal, Section 5). In the context of the Australian data relied upon by the ERG, it is self evident that the mean BSA of patients from Australia may not reflect that of UK patients suffering from the same diseases.

- Furthermore, the Australian data, relied upon by the ERG, were not limited to patients with NSCLC, but were taken from patients with a range of malignancies, including cancers of the prostate and breast. It is reasonable to assume that patients receiving second-line treatment advanced NSCLC have a lower BSA. The ERG provides no explanation for its assumption that these data may represent the situation of patients with NSCLC.

The figure in respect of mean BSA, relied upon for the purposes of economic modelling, makes a substantial difference to the ultimate ICER obtained. The ERG's assumption of a mean BSA of 1.83m^2 in patients eligible for second-line treatment for NSCLC meant that the distribution would include a proportion of patients who have a BSA of over 2m^2. As a result of this distribution, the ERG estimated an average of 2.21 vials per cycle. This means that in a percentage of patients a third vial of pemetrexed disodium is required for every cycle of treatment, as compared with the mean BSA proposed by Lilly, which would require no more than two vials per cycle. As no more than 2 vials are used per cycle, the ERG distribution should have been truncated at 2m^2. The impact of assuming 2.21 vials per cycle increases the pemetrexed drug costs from £1360 (based on the Lilly estimates of 1.7m2) to £1768 (ERG estimate). An increase of £408 for pemetrexed will clearly have a significant impact on the ICER when drug costs contribute over 50% of the total direct costs.

The Appraisal Committee accepted that Lilly's estimate was "appropriate", but then concluded that "this factor would not substantially change the ICER" (paragraph 4.6 of the FAD). No explanation for this conclusion is provided, despite the fact that the Appraisal Committee's acceptance of Lilly's approach means that the costs of pemetrexed disodium treatment used by the ERG should be reduced by one third. In the context of the significant effect of drug costs on the ICER (the drug costs represent more than half of the costs associated with treatment with pemetrexed disodium), a change in costs of this magnitude would be expected to result in a substantial improvement in the cost effectiveness and the basis for the Appraisal Committee's assumption therefore requires explanation.

2.1.2.2 <u>The adjustments made by the Expert Review Group in respect of utility gains during the comparison with docetaxel are unexplained</u>

In its assessment of the economic model for pemetrexed disodium, submitted by Lilly, the ERG suggests modification to the calculation of utility benefits associated with pemetrexed disodium compared with docetaxel treatment. The LRiG states, at page 44 of its report:

> "*The overall utility gain claimed for pemetrexed over docetaxel has been re-estimated after applying a half cycle correction (not used in the company model), and then disaggregated into components attributable to modelled survival gain, and treatment-related adverse effects*".

However the changes made by the ERG and the reasons for them are unclear from the report. In particular, the reduction of the utility estimate used from 0.07 to 0.0034 cannot be explained by corrections and adjustments made by the ERG. This represents a 100-fold reduction in Lilly's utility estimates and it is not clear how 0.0034 represents the utility benefit of avoiding significant toxicities. Lilly therefore asked the Institute to provide clarification of the recalculation undertaken by the LRiG, so that the company could understand and replicate the analysis. The Institute's response of 15 November 2006 stated merely that:

> "*Having checked with the technical team on this occasion, the ERG has not made adjustments to the "utility data" when presenting their illustrative scenario*".

This explanation is inconsistent with the clear statement from LRiG and the results presented in the ERG report and relied upon by the Appraisal Committee (paragraphs 3.8 and 4.5 of the FAD). Lilly has accordingly been provided with no proper explanation of the analysis undertaken by the ERG and has been prejudiced in its ability to understand and comment upon the conclusions reached by the Appraisal Committee.

2.1.2.3 <u>It is unclear how the Appraisal Committee took into account the quality of life effects of adverse events associated with docetaxel therapy, when these were not captured by the measure used in the JMEI randomised controlled clinical trial</u>

A substantial advantage of pemetrexed disodium therapy over docetaxel is the very substantial reduction in the incidence of neutropenia associated with treatment. In the JMEI randomised controlled trial which compared the two treatments, 40.2% of patients who received docetaxel developed a grade three or four neutropenia[3], as compared with 5.3% patients who received pemetrexed disodium. This resulted in significantly more patients in the docetaxel arm (13.4%) being hospitalised for neutropenic fever during the course of the study as compared with the pemetrexed arm (1.5%). While other adverse effects (including nausea, vomiting and fatigue) occurred with similar frequency between the two groups, the incidence of alopecia was significantly higher and there was a trend towards higher rates of grade three and four diarrhoea in patients receiving docetaxel.

The substantial benefits of pemetrexed in terms of reduced toxicity would be expected to translate into improved quality of life (QoL) as compared with patients treated with docetaxel. However it is unclear how such benefits have been taken into account by the Appraisal Committee in considering pemetrexed.
In its assessment of pemetrexed, the ERG concluded that there was almost no difference in health related quality of life between the two treatments. The reason for this was that the JMEI trial had not demonstrated differences in efficacy or in the Lung Cancer Symptom (LCSS) scale, used in the trial, between the docetaxel and pemetrexed groups. However, the LCSS is not a (QoL) is used to measure impact on symptoms of the disease and does not consider side effects of treatment; it therefore fails to recognise the quality of life effects of the substantial increase in neutropenia, the associated hospitalisations and other adverse events (such as alopecia) associated with docetaxel therapy. Furthermore, the LCSS

[3] Defined using the National Cancer Institute Common Toxicity Criteria, version 2

was administered in JMEI while patients were receiving treatment, rather than subsequently, when most adverse events were experienced, so the impact of such effects on health related quality of life in toxicities could not be captured.
At paragraph 3.4 of the FAD, the Appraisal Committee noted that the JMEI study reported no difference between docetaxel and pemetrexed in terms of health related quality of life, although no reference is made to the limitations of those data, as described above. At paragraph 4.3, the FAD refers to adverse effects and states "*The Committee also heard that some patients may prefer pemetrexed to docetaxel because of its different side-effect profile, particularly the lower rate of alopecia. However, the clinical specialists considered that patients undergoing second-line chemotherapy treatment usually valued other effects of treatment more highly, in particular increased life expectancy and overall quality of life".*
While, in its response to comments received in relation to the ACD, NICE accepted that LCSS does not take into account the quality of life effects resulting from treatment related adverse events, there is no indication from these comments or from the FAD itself, how the benefits of pemetrexed, in terms of reduced toxicity, have been taken into account by the Committee in assessing the "overall quality of life" referred to at paragraph 4.3 of the FAD.

2.1.2.4 <u>No explanation is provided for the Appraisal Committee's conclusion that patients who are unable to receive docetaxel might not respond to pemetrexed</u>

At paragraph 4.9 of the FAD the Appraisal Committee comments that the JMEI randomised controlled clinical trial did not assess use of pemetrexed disodium in patients who were unable to receive docetaxel and "it was therefore concerned that the clinical effectiveness of pemetrexed had not been established in this context".

However, pemetrexed disodium has a different mechanism of action to docetaxel and there is accordingly no reason why a patient who is unable to receive docetaxel should be similarly precluded from receiving pemetrexed. The Appraisal Committee has provided no reasons to explain its concern and, in the absence of reasons, consultees are unable appropriately to respond to the statement in the FAD.

Furthermore, the same Appraisal Committee adopted a different approach when considering erlotinib and the requirement for a clear explanation in this case is therefore heightened. The principal trial of erlotinib was undertaken in patients who were unable to receive chemotherapy. However, for the purposes of its appraisal, the Appraisal Committee accepted a comparison of docetaxel to erlotinib, even though the effectiveness of erlotinib in patients who are able to receive chemotherapy has not been formally established.

2.1.3 <u>NICE has not explained how it has considered the relevant additional factors provided in its procedures for cases where the cost per QALY exceeds £20,000</u>

At paragraphs 4.10 and 4.11 of the FAD, the Appraisal Committee considered the cost-effectiveness of treatment with pemetrexed disodium in circumstances where the patient was unable to receive docetaxel. The Appraisal Committee expressed the view that the ICER for pemetrexed compared with BSC was between £40,000 and £60,000. However, the FAD states at paragraph 4.12:

> *"The Committee concluded that pemetrexed would not be a cost-effective use of NHS resources when compared with either docetaxel or BSC."*

While Lilly believes that the ICERs relied upon by the Appraisal Committee are incorrect and inappropriately pessimistic, there is in any event no explanation in

the FAD for the conclusion at paragraph 4.12. It is therefore unclear whether and if so how, NICE took into account the additional factors listed in its Guide to the Methods of Technology Appraisal as having particular application where the cost per QALY was greater than £20,000. Section 6.2.6.10 of the Guide states:

> *"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use for NHS resources are more likely to make more explicit reference to factors including:*

- the degree of uncertainty surrounding the calculation of the ICER
- the innovative nature of the technology
- the particular features of the condition and population receiving the technology
- where appropriate, the wider societal costs and benefits."

Therefore in reaching any judgement about whether or not it is appropriate to make a recommendation for use of a product in NHS patients, where the ICER is likely to exceed £20,000, NICE is required to take into account the listed factors. Without any explanation in the FAD as to whether and if so how such factors have been considered by the Appraisal Committee in this case, it is impossible for Lilly properly to assess the Appraisal Committee's conclusions.

The requirement for NICE to provide a reasoned explanation for its conclusions is particularly acute in view of the fact that, in general, pemetrexed disodium scores very highly in relation to all of the additional factors, in particular.

- Pemetrexed is innovative; it is the first cancer medicine to be available that acts on at least three distinct enzyme target sites.

- The clinical need of the patients with the disease under consideration is considerable. NSCLC is a common cancer with a poor prognosis. For patients who relapse following first line treatment for their condition there are few licensed alternatives and the associated toxicity may limit choice still further. There is a real need for new and innovative treatments in this patient population.

2.2 Ground Three: Excess of Powers

2.2.1 The conclusion by the Appraisal Committee that the results of non-inferiority testing do not exclude the possibility of a marginal loss of efficacy compared with docetaxel, is inconsistent with the marketing authorisation granted by the European Commission

As indicated above (section 1.1), pemetrexed disodium was granted an authorisation by the European Commission following a favourable opinion issued by the CHMP. The scientific conclusions which formed the basis for that authorisation are summarised in the EPAR, which states, in relation to the pivotal JMEI trial, "*although non-inferiority was not formally demonstrated, the data are robust enough to conclude that a clinically significant inferiority of pemetrexed to docetaxel in terms of efficacy in this population are unlikely*".

However, the FAD issued by NICE in relation to pemetrexed disodium for the treatment of NSCLC indicates that the Appraisal Committee placed weight on the fact that non-inferiority was not formally excluded, rather than the overall conclusions of the CHMP. Paragraph 4.2 of the FAD states simply " …*the results of non-inferiority testing did not formally exclude the possibility of a marginal loss of efficacy of pemetrexed when compared with docetaxel*".

The suggestion by the Appraisal Committee, which appears to have influenced its conclusions, that pemetrexed may be less efficacious than docetaxel, is inconsistent with the overall assessment of the CHMP and the authorisation for pemetrexed. Such a conclusion is outside NICE's remit and represents an excess of its powers.

3 Requested Actions

Lilly therefore respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee with the following Directions:

- That all the evidence relied upon by the Appraisal Committee in formulating its conclusions should be disclosed to consultees and that the reasoning for their conclusions should be fully explained.
- That the Appraisal Committee should obtain perspectives from three clinical experts with experience in using pemetrexed disodium for the treatment of patients with NSCLC and that their written views, addressing the matters of interest to NICE in the context of this appraisal, should be disclosed to consultees.
- That the approach of the Appraisal Committee to this appraisal should be consistent with that followed in other appraisals, specifically that of erlotinib.

Yours sincerely

Head of HTA and Health Outcomes, Lilly UK