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Dr Carole Longson
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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 MALIGNANT PLEURAL MESOTHELIOMA

Eli Lilly and Company Limited (Lilly) has considered the Final Appraisal Determination (FAD) prepared by the Institute and submits this appeal in relation to the procedures followed during this appraisal and the substantive conclusions of NICE's Appraisal Committee. Lilly requests a hearing before NICE's Appeal Panel for the determination of its appeal.

1. Introduction

1.1 History of the appraisal process

Pemetrexed disodium (Alimta®) is a multi-targeted antifolate, indicated, in combination with cisplatin, for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma. It is the subject of a marketing authorisation granted by the European Commission on 20 September 2004 following a favourable decision by the CHMP issued on 23 June 2004.

The final Scope for this appraisal by NICE was issued in May 2005 and stated, as its objectives: "*To appraise the clinical and cost effectiveness of pemetrexed disodium (Alimta, Eli Lilly) for the treatment of unresectable malignant pleural mesothelioma in chemo-naïve patients and to provide guidance to the NHS in England and Wales*".

Lilly's submission to NICE in relation to pemetrexed disodium was sent to the Institute on 1 August 2005.

The Liverpool Reviews and Implementation Group (LRiG) was commissioned on behalf of NICE to prepare an Assessment Report in relation to the use of pemetrexed disodium in patients with malignant pleural mesothelioma and its report was circulated to Lilly and other consultees on 10 January 2006. Lilly submitted comments on the Assessment Report to NICE on 7 February 2006.

The Appraisal Committee met for the first time to consider these technologies on 7 March 2006. Following this meeting an Appraisal Consultation Document (ACD) was prepared and circulated to consultees. Lilly submitted its comments on the ACD to NICE on 26 April 2006. The Appraisal

Committee met for a second time on 10 May 2006 and, following this meeting, the Final Appraisal Determination (FAD) was prepared.

1.2 Use of pemetrexed disodium for the treatment of malignant pleural mesothelioma

Lilly assumes that the members of the Appeal Panel will have varying degrees of knowledge of this therapeutic area and therefore provides a brief summary of the situation of patients with malignant pleural mesothelioma and the use of pemetrexed disodium. This summary should not however be viewed as replacing the more detailed information provided in Lilly's original submission of 1 August 2005.

The annual number of mesothelioma deaths estimated for 2005/2006 is 2,298 in the UK. The estimates for England in the same year is 1,605 deaths and in Wales this is estimated at 60 deaths. The typical patient is male and relatively young, being aged about 60 years at diagnosis. In the overwhelming majority of cases the tumour develops some 30-60 years after exposure to asbestos. The early symptoms are relatively non-specific and insidious, resulting in delayed presentation and diagnosis. As a result approximately 88% of patients have advanced disease, with a poor prognosis, by the time the diagnosis is reached. Pleural mesothelioma may be staged histologically as epithelioid, sarcomatous or biphasic and clinically, using the TNM system, by reference to the extent of the primary tumour and the presence of tumour in local lymph nodes and distant metastases.

Symptoms associated with malignant pleural mesothelioma include chest pain (resulting from lung or chest wall invasion or nerve or vertebral involvement) dyspnoea as the spreading tumour prevents lung expansion, weight loss, cachexia and night sweats.

The estimated incidence of mesothelioma is expected to increase to a peak of 1,950 to 2,450 people per year between 2011 and 2015[1]. Of these patients, some 88% (currently some 2,022 patients per year) have advanced disease at presentation, with unresectable tumours; these are the patients who are potentially eligible for pemetrexed disodium therapy. At present however, only 49% of such patients receive chemotherapy treatment and the remainder are managed with active symptom control (ASC) or best supportive care (BSC). Of the patients who receive chemotherapy, some 50% are treated in the context of randomised controlled trials.

Pemetrexed disodium is the only treatment, authorised in the UK that has demonstrated efficacy in patients with malignant pleural mesothelioma in clinical trials. There is no established alternative treatment, although patients may receive a variety of other cytotoxic agents including cisplatin alone, vinorelbine (+/- platinum) or a combination of mitomycin C, vinblastine and cisplatin (MVP).

2. *Grounds of Appeal*

Lilly appeals the draft guidance in the FAD on the following grounds:

- The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
- The Institute has prepared guidance which is perverse in the light of the evidence submitted;
- The Institute has exceeded its powers.

[1] Hodgson et al 2005

3. *Ground 1: The Institute has failed to act fairly and in accordance with its published procedures.*

3.1 <u>The Institute has failed to show transparency in the appraisal process.</u>

NICE has, quite properly, recognised from its inception that its decisions should be fully transparent, both in terms of the evidence relied upon in formulating guidance and the reasoning by which its conclusions are reached. This requirement for transparency is essential, as a matter of fairness in accordance with English administrative law, in compliance with the provisions of the Transparency Directive (Directive 89/105/EEC) and to ensure that its decisions are credible.

However, despite these requirements and NICE's commitment to transparency, Lilly believes that this appraisal has not met the relevant standards. The evidential basis and reasoning for the determination are unclear and this situation has hampered the ability of Lilly to participate in the appraisal process. Furthermore, in the absence of proper explanations to justify the conclusions of the Appraisal Committee, clinicians seeking to apply NICE's recommendations will be unable to assess how these apply to their patients.

Lilly refers below to areas where it has particular concerns in relation to lack of transparency:

3.1.1 <u>The Appraisal Committee's reasons for rejecting the sub-group of patients who respond to treatment with pemetrexed disodium plus cisplatin are unclear.</u>

At paragraph 4.3.9 of the FAD, the Appraisal Committee refers to the fact that not all patients respond to treatment with pemetrexed disodium plus cisplatin and notes that, in the Evaluation of Mesothelioma in a Phase III trial with Alimta and Cisplatin (EMPHACIS) trial, 87% of those who responded had done so within four cycles. The FAD states that the Committee considered the possibility that the cost effectiveness of pemetrexed disodium plus cisplatin might reach an acceptable level, if treatment were to be discontinued in patients who had not responded to treatment after four cycles of therapy. While the Committee went on to reject making any recommendation in respect of the sub-group of patients who demonstrate such response, the reasons given are unclear.

- The FAD states that the Appraisal Committee "was not persuaded that the savings that might be made would be sufficient to render the technology cost effective...". It is unclear from this statement whether the Appraisal Committee made any attempt to assess the cost effectiveness of pemetrexed disodium in circumstances where patients who failed to respond to treatment received no further therapy after four cycles. In circumstances where treatment costs in patients who fail to respond to treatment are reduced, the effect on the cost effectiveness assessment must be favourable; any failure by the Appraisal Committee properly to consider and investigate the effect of such costs savings would be procedurally unfair. The current wording of the FAD provides no explanation for the Appraisal Committee's conclusion and whether proper consideration was given to this issue.

- The Appraisal Committee also states that it concluded there was insufficient evidence that the survival benefit achieved in the EMPHACIS trial could be obtained using a treatment strategy whereby patients who showed no response after four cycles received no further therapy. No explanation for this surprising conclusion is provided, even though it appears inconsistent with the clinical trial data. The data from EMPHACIS demonstrates that the survival gain seen in the 87% of patients who responded to pemetrexed disodium and cisplatin within four cycles was significantly greater than for those patients who did not respond. The median survival for patients who responded to pemetrexed disodium plus cisplatin was 18.4 months, compared to 14.8 months for cisplatin responders, whilst the survival for non-responders did not differ between the treatment arms (8.2 versus 8.1 months). The hazard ratio (responder versus non-responder) for pemetrexed disodium plus cisplatin was 0.31 (C.I. 0.22-0.45). These results provide powerful evidence that the discontinuation of treatment in patients who have not shown a response after four cycles does not reduce the overall survival benefits seen in

the final population and Lilly simply does not understand the conclusion of the Appraisal Committee that there was insufficient evidence that the survival benefit achieved in the EMPHACIS trial could be obtained using this treatment strategy.

Survival analysis for responders vs non-responders, EMPHACIS ITT population (N=448)

		Pem/cis n=226		Cis n=222
Responders	N	94		37
	Median	18.4		14.8
	% censored	56		49
HR (pem/cis vs cis)			.71	
95% CI			(.41-1.22)	
Non-responders	N	132		185
	Median	8.2		8.1
	% censored	21		24
HR (pem/cis vs cis)			1.09	
95% CI			(.84-1.40)	
HR (responder vs non-responder) 95% CI		.31 (.22-.45)		.41 (.29-.76)

- Finally, the Appraisal Committee express the view that tumour response criteria are ill defined in mesothelioma and that the site and mode of spread of the disease make accurate measurement of tumour response difficult. Again, the basis for this statement is unclear and the Appraisal Committee provides no explanation for its conclusion. In the EMPHACIS study, patients were assessed for a complete response (complete disappearance of all disease) or a partial response (by reference to measurable disease lesions); in measuring a partial response, at least a 50% decrease in the sum of the products of bidimensionally measurable disease or a decrease in at least 30% in the sum of the greatest diameter of unidimensionally measurable lesions was required. This strategy was reported and published in peer review journals[2] and represents a clear and readily ascertained measure to determine response to treatment. The results demonstrate a clear demarkation between the responders and non-responders and the fact that this could readily be identified by the investigators; it does not represent subtle or ambiguous changes in tumour appearance. In these circumstances, Lilly does not understand why and on what basis the Appraisal Committee expressed the view that tumour response criteria are not well defined or would be problematic to determine in clinical practice. The conclusion is also significant in the context of the Appraisal Committee's emphasis on the MS01 trial, where, presumably, the same issue would apply.

Lilly therefore believes that the reasons given by the Appraisal Committee for rejecting the responder subgroup are inadequate and that further reasoning is required to explain why the Appraisal Committee did not recommend treatment with pemetrexed disodium, consistent with UK clinical practice, in such patients.

3.1.2 NICE has not explained its reliance upon mean, rather than median, survival data for the cost effectiveness assessment of pemetrexed disodium

While the Appraisal Committee has, consistent with the standard approach in the assessment of oncology medicines, relied upon median survival, associated with pemetrexed disodium treatment, to appraise clinical benefit (paragraphs 4.1.4 and 4.1.5 of the FAD), it has only used mean survival values, estimated from the EMPHACIS trial data using Kaplan-Meier curves (paragraph 4.2.3 of the FAD), in the cost effectiveness evaluation.

[2] Vogelzang et al 2003.

In terminal diseases, such as malignant pleural mesothelioma, the survival time data is subject to a strong right-hand skew (i.e. a long right hand 'tail' of distribution). Therefore, the mean estimate of survival time is strongly influenced by the tail of the distribution, but commonly this distribution is not well estimated due to the level of censoring (non-random missing data). In EMPHACIS, the overall censoring rate at the time of the initial analysis for the intention to treat (ITT) population was 32.1% and, for the fully supplemented (FS) cohort, it was 40.2%. This equates to 143 and 180 cases of censored survival data for the ITT and FS populations respectively. This results in the mean survival times for treatment (and therefore the difference between treatments, which leads to the ICER) being highly uncertain in comparison to the median survival times. The median disregards the extremes of distribution and is therefore associated with a greater degree of certainty. It was considered to be more representative of the typical patient outcomes for the purposes of trial analysis in EMPHACIS and for regulatory approval. This is consistent with the majority of phase III oncology trials, which report only median survival times as the most robust estimate of survival gain and therefore estimating a mean for comparator treatments (e.g. MVP and vinorelbine in this Appraisal) is also subject to great deal of uncertainty in this appraisal.

In the context of this appraisal, Lilly included mean survival estimates in its original submission, at the insistence of the Assessment Group, as well as estimates based upon the median. However, in light of the degree of uncertainty surrounding the mean, consideration should have been given to the ICERs produced using median values as well as means. Such an approach would also be consistent with that followed in other oncology appraisals, where the Assessment Groups and Appraisal Committees have assessed cost-effectiveness using median survival values. It is moreover unclear whether and, if so, to what extent the Appraisal Committee took into account the uncertainty in the cost effectiveness estimate of pemetrexed disodium resulting from its use of mean survival data when more robust data based upon the median was also available.

The Scottish Medicines Consortium (SMC) accepted pemetrexed for use in mesothelioma the NHS in Scotland in May 2005, based on cost effectiveness calculated using median survival data (see also 3.1.5).

3.1.3 The Appraisal Committee provide no explanation for their conclusion that pemetrexed disodium plus cisplatin is very unlikely to be cost effective when compared with other treatments, even though the Assessment Group concluded that the evidence base for such other technologies is too weak to be taken seriously as the basis for decision making.

At paragraph 4.3.6 of the FAD, the Appraisal Committee concluded "*that pemetrexed disodium plus cisplatin was very unlikely to be cost effective when compared with MVP, vinorelbine or ASC/BSC*". No explanation for this surprising conclusion was included in the FAD and the reasoning of the Appraisal Committee is therefore unclear. As indicated above, no other treatments are authorised for the treatment of malignant pleural mesothelioma and no other therapy has been adequately investigated in this indication. The situation was confirmed by the Assessment Group who indicated "*the evidence base for estimating survival in other comparators (including supportive care) is too weak to be taken seriously as a basis for decision making.*"

For the avoidance of doubt, while Lilly had submitted a cost effectiveness assessment which attempted to use such data for comparative purposes, that submission was made at the request of the Institute. Lilly believes that the data relating to all comparative treatments are weak and that reliance upon them to form a conclusion such as that made by the Institute at paragraph 4.3.6 of the FAD, requires proper explanation. That is lacking in this case.

3.1.4 NICE has failed to disclose any written perspectives prepared by [redacted], a clinical specialist who attended the meetings of the Appraisal Committee.

NICE's procedures provide that the patient experts and clinical specialists who attend the Appraisal Committee meetings will provide a written perspective of their views (paragraph 4.5.1.4 of NICE's

Guide to the Technology Appraisal Process). These written perspectives are then included in the evaluation report made available to the Appraisal Committee and subsequently circulated to consultees. The provision of such written perspectives provides a written indication of the views of such experts and the oral evidence that they provide at the meetings of the Appraisal Committee. Proper standards of transparency require that the evidence relied upon by the Appraisal Committee, including the evidence of invited experts, should be disclosed to consultees. That standard is also reflected, in the case of the evidence of clinical specialists invited to advise the Appraisal Committee, in NICE's procedures.

It is self evident that the evidence of clinical specialists, selected specifically because of their particular expertise in the relevant therapeutic area, is likely to be highly influential in any appraisal. In these circumstances, Lilly believes that the requirement to disclose the substance of the evidence provided by such clinical specialists is heightened.

In the context of this appraisal however, while [redacted] attended the meeting of the Appraisal Committee on 7 March 2006 as a clinical specialist, her written perspectives have not been disclosed to Lilly. The company has no opportunity to comment upon any of the observations made by [redacted] and has no knowledge of how these may have influenced the Appraisal Committee in reaching its conclusions. This is a matter of particular concern in the context of the matters raised at paragraph 3.5 below.

Lilly believes that [redacted] was required to produce written perspectives setting out her views with respect to pemetrexed disodium in accordance with NICE's procedures and principles of transparency and that NICE was required to disclose such written perspectives to consultees, so that these could be subject to proper scrutiny and comment. That has not occurred in this case.

3.1.5 No explanation is given for NICE's divergence from the conclusions of the Scottish Medicines Consortium.

In May 2005, the Scottish Medicines Consortium carried out an assessment of clinical and cost effectiveness of pemetrexed disodium in the treatment of malignant pleural mesothelioma. The SMC recommended the product, in combination with cisplatin, on a restricted basis, within NHS Scotland for the treatment of chemotherapy-naïve patients with stage III/IV unresectable malignant pleural mesothelioma. While Lilly recognises that NICE must carry out its own appraisal of each technology, in view of the fact that the work of the SMC was conducted in the UK within an NHS context and that the effect of NICE's decision will be that SMC recommendations are overruled and pemetrexed disodium will be withdrawn as a treatment option for Scottish patients, we believe it is incumbent upon NICE to provide a reasoned explanation to justify a divergence from the conclusion of SMC.

3.2 Failure to consider the benefits of pemetrexed disodium by reference to the cost per life year gained (LYG) is discriminatory

The cost effectiveness assessment included in the FAD, focuses exclusively on calculations based on cost per QALY gained. While Lilly is aware that NICE prefers to assess all technologies using this approach, the Institute also recognises that such an approach does not result in a fair comparison between all therapeutic areas. In particular, reliance upon a standard cost-utility-analysis (based upon quality adjusted life years (QALYs)) may discriminate against persons with a short life expectancy, the elderly and those with terminal illnesses. The use of QALYs to assess the cost effectiveness of treatments for conditions such as malignant pleural mesothelioma is therefore controversial.

Cost-effectiveness analysis, using cost per LYG estimates, is particularly relevant in this case because no utility estimates exist for mesothelioma, a rare disease. The Lilly model used

advanced lung cancer utility estimates based upon survival and adjusted these only by performance status. The benefits of symptom relief and the improvements in quality of life for pemetrexed/cisplatin patients were not included in the QALY estimates. However, as stated in the submission, this means the QALY gain estimated for pemetrexed/cisplatin was conservative and underestimated the real QALY gain for these patients. Therefore the cost per LYG is a valuable additional estimate of cost-effectiveness and should be considered by the Appraisal Committee.

NICE's procedures recognise this situation. NICE's "Guide to the Methods of Technology Appraisal" states, at paragraph 5.3.4.2, "*If the assumptions underlying QALYs (for example, constant proportional trade-off and additive independence between health states) are considered inappropriate in a particular case, then evidence to this effect should be produced and analyses using alternative measures may be presented as a non-reference case analyses".* Similarly, the Chairman and Vice Chairman of the Institute stated in a paper published in the British Medical Journal[3] that measures other than QALYs would be used in appropriate cases, particularly where appropriate utility values are not available. Therefore in other appraisals of oncology treatments NICE has considered the benefits of therapy in terms of cost per LYG (e.g. Capecitbine for the treatment of breast cancer, imatinib for the treatment of chronic myeloid leukaemia).

In the context of treatment for malignant pleural mesothelioma, prolonging survival is considered the most important aim of treatment. Accordingly, at the information meeting for consultees held on 15 June 2005, Professor David Barnett, from the Appraisal Committee, indicated that a cost per life year gained evaluation was important in this therapeutic area and should be included in the analysis. In these circumstances, we believe, consistent with the statements made by the Chairman and Vice Chairman of the Institute and the approach followed in other appraisals, that the Appraisal Committee was bound to consider a cost effectiveness evaluation of pemetrexed disodium by reference to cost per life years gained and to explain its consideration of such evaluation, in the FAD.

3.3 NICE's adherence to a fixed cost effectiveness threshold is unfair and inconsistent with their process and the approach followed in relation to other technologies

Lilly believes that the cost effectiveness values generally used to determine whether a technology should be recommended for use in NHS patients are inappropriate in this case and that the Appraisal Committee should, as a matter of fairness, exercise its discretion to take into account other factors in the context of a higher threshold value, including the clinical need of patients with malignant pleural mesothelioma, the absence of other therapies with demonstrated effectiveness in this indication and the rarity of the condition.

NICE has stated that particular consideration is required where the cost-effectiveness assessment of a technology exceeds the threshold of £30,000 per QALY and that such products should be recommended for use in NHS patients where there is uncertainty surround the calculation of the ICER, the technology is innovative, the clinical need of the patients with the condition under consideration is high and, where appropriate, the wider societal costs and benefits support such usage. Pemetrexed/cisplatin meets all of these requirements for a special case to be made:

- there is uncertainty surrounding both use of the mean survival estimates and also in terms of the utilities used to calculate QALYs;
- this is the first and only medicine licensed and tested for the treatment of the condition under consideration;
- the affected patients suffer from a rare and devastating industrial disease

[3] Rawlins & Culyer. National Institute for Clinical Excellence and its Value Judgments. BMJ 2004; 329:224-226

- the societal benefit of providing this medicine would be high whilst the costs are comparatively low and time-limited due to the small number of expected patients.

We believe that insufficient consideration was given to these additional factors that have been laid down by the Institute to ensure equitable decision making for patients in the UK. The Appraisal Committee has been prepared to follow such an approach in relation to certain other similar technologies and fairness requires that pemetrexed disodium and patients with malignant pleural mesothelioma are treated in a consistent way.

The clinical benefits of treatment with pemetrexed disodium plus cisplatin are established (paragraph 4.1.9 of the FAD) and NICE has accepted that it:

- prolongs survival by at least 3 months, compared with cisplatin alone
- improves one year survival,
- increases time to progressive disease,
- improves tumour response rate and
- improves quality of life and disease and symptom control.

With respect to cost effectiveness, Lilly believes the Institute's conclusions are pessimistic; NICE has calculated a cost per QALY gained as a result of pemetrexed disodium treatment of £37,664 - £60,561 (paragraph 4.2.9 of the FAD). It is of note that, if the ICERs provided by Lilly, based upon median estimates of survival had been used and a cost-effectiveness analysis approach followed (i.e. cost per life year, rather than cost-utility analysis), the ICERs would have ranged from £19,101 - £34,393.

The cost per QALY estimates quoted in paragraph 4.2.9 of the FAD are similar to those for riluzole, recommended by NICE for the treatment of motor neurone disease (amyotrophic lateral sclerosis). Like pemetrexed disodium, riluzole is associated with a survival gain of between two and four months in patients with a very short life expectancy, and a cost per QALY of between £34,000 and £43,500 was calculated during the course of NICE's appraisal in 2001. Allowing for the effects of inflation these values are comparable with those applicable to pemetrexed disodium.

Both motor neurone disease and malignant pleural mesothelioma are rare conditions and the impact on the NHS of a positive recommendation from NICE would be similar. The additional costs to the NHS of recommending riluzole treatment were assessed in 2001 as being in the region of £5 million.

NICE has estimated the cost of pemetrexed disodium treatment at £8,000 per patient, based on an average of five cycles of therapy per patient and a body surface area of 1.8m² (paragraph 3.4 of the FAD). Based on these figures and assuming a favourable 55% usage of pemetrexed disodium in eligible patients who receive chemotherapy outside the clinical trial context, Lilly estimated the total cost to the NHS to be £3.4 million for the financial year 2006/2007. Similarly, the Assessment Group, assuming that all patients eligible for treatment with pemetrexed disodium would receive therapy, and projecting future use, commented that "given the relatively small number of patients with mesothelioma, albeit increasing, the overall budget impact of pemetrexed would be unlikely to be no more than £5 million per year."

In the context of the very high clinical need of patients with malignant pleural mesothelioma and the absence of any other product, licensed for the treatment of their condition and in the context of the relatively low aggregate costs that might be expected should NICE recommend use of pemetrexed

disodium in some or all eligible patients, we believe that a relaxation of the rigid £20,000-30,000 QALY value adopted as a threshold for NICE recommendations, should be followed here. Such an approach would be consistent with that followed by NICE in the appraisal of riluzole for the treatment of motor neurone disease in 2001 and reaffirmed without modification in April 2006. In reaching its conclusion in 2001, the Appraisal Committee stated that it "*took account of the severity and relatively short life span of people with amyotrophic lateral sclerosis and, in particular, as directly reported to it, the values which patients place on the extension of tracheostomy free survival time. With these considerations in mind, the Committee considered that the net increase in cost for the NHS of the use of riluzole in this indication was reasonable when set against the benefit, as extended months of an acceptable (to patients) quality of life*".

The situations of the patients who are eligible for treatment with these two products are strikingly similar. Lilly believes that fairness requires consistency in approach between patients with severe disabling terminal diseases where similar benefits may be obtained from treatment with similar cost effectiveness and aggregate costs. NICE maintains that it aims to treat products and patients fairly by following an approach that enables comparisons on value to be made between technologies in different therapeutic areas. In this case, that aim has not been achieved; the inconsistency in approach followed in this appraisal to that in other appraisals is accordingly unfair to patients with malignant pleural mesothelioma and to Lilly.

3.4 The numbers of members of the Appraisal Committee who attended the meetings on 7 March and 10 May was inadequate to permit proper consideration of this technology

This Appraisal has been considered by Appraisal Committee B, which was comprised, at the date of the first meeting of the Appraisal Committee on 7 March 2006, of 31 members including the Chairman, Professor Andrew Stevens. However, while the Committee has 31 members, the meeting on 7 March, was attended by only 15 of them; less than half of the Committee was present.

Similarly, at the meeting on 10 May 2006, only 18 members (one of whom, Roderick Smith, is not listed as a member on the NICE website or on the FAD) of the Committee attended but only 9 of these were at the previous meeting, 2 of whom were the chair and vice-chair.

In circumstances where a decision is to be made by a Committee, it is self evident that proper procedures require that members of the Committee are present and contribute to the discussion. On any view, a meeting at which less than half of the members attend cannot be quorate and Lilly believes that the spread of expertise present at the hearing was also adversely affected, such that the Appraisal Committee was not in a position to make a fair decision with respect to the use of pemetrexed disodium.

3.5 The Appraisal Committee failed to take into account the potential conflict of interest arising from the involvement of the clinical specialists in the MSO1 trial

It is a fundamental principle of fairness under English administrative law that a tribunal determining the rights of any person must be impartial and free from bias. In this context, it is insufficient for actual bias to be absent; the test is, instead, that a reasonable person aware of the circumstances would not conclude that there was a reasonable appearance of bias. It is for this reason, that members of NICE's Appraisal Committee and experts invited to advise the Committee, are required at every meeting, to declare any interests that might appear to affect their impartiality in the context of the appraisal.

While NICE's procedures adopt a narrow approach to the types of interests that should be declared (essentially limiting these to payments from the healthcare industry benefiting either an individual or his department), decisions of NICE's Appeal Panel confirm that broader interests including

involvement in competing research, should also be declared (decision of the Panel following the appeal against the FAD for paclitaxel for ovarian cancer, 12 November 2002). Moreover, MHRA's Code of Practice on Interests for Chairman and Members of the Commission on Human Medicines, Certain Section 4 Committees and Expert Advisory Groups makes clear that interests which may influence or appear to influence the impartiality of an expert extend to research work relating to a particular product or class of products, (even though the research has not been funded by any particular pharmaceutical company) and where an individual has made public statements about a particular company, product or class of products. Lilly believes that this is manifestly the correct approach and should be applicable equally to NICE as to the bodies subject to the MHRA Code. It is clear that interests other than payments received from pharmaceutical companies may affect the impartiality of members of the Appraisal Committee and expert advisers and these should be clearly stated and transparent.

However, in the context of this appraisal, while both the clinical specialists [redacted] and [redacted] are investigators in the MSO1 Study, there is no reference to any declaration to this effect in the minutes of the Appraisal Committee meeting or other information disclosed in relation to the Appraisal Committee's deliberations.

While there is no standard treatment regime for the treatment of malignant pleural mesothelioma and no treatment authorised for this condition, other than pemetrexed disodium, the MSO1 Study compares the effects of certain chemotherapeutic agents that may be used in the UK for this indication. The MSO1 Study accordingly considers the effects of vinorelbine and MVP regimens and compares these with best standard care/active symptom control; the study does not include patients treated with pemetrexed disodium. The MSO1 Study is due to complete recruitment in 2006 and to report its findings in 2007. It is therefore clear that any guidance issued by NICE with respect to the use of pemetrexed disodium could influence the ability of the investigators to continue the study. This situation was recognised by the Assessment Group, who stated "*Given that this trial also addresses the important question of whether any chemotherapy is better than supportive care, it would be unfortunate if this trial could not be carried on as a consequence of the pemetrexed plus cisplatin trial or a NICE Appraisal*".

While Lilly has no concerns regarding the integrity of [redacted] and [redacted] in the circumstances, it is clear that an impartial observer would conclude that there was a risk that an investigator in the MSO1 Study would have an interest in pemetrexed disodium not being recommended for use in NHS patients because such a recommendation could prejudice the completion of MS01. This situation creates a substantial conflict of interest between a specialist acting as advisor to the Appraisal Committee and his/her role as study investigator. Lilly believes that this conflict of interest and the failure properly to disclose it represents a serious flaw in the appraisal process and taints the conclusions of the Appraisal Committee.

4. *Ground 2: The FAD is perverse in the light of the evidence submitted.*

4.1 <u>The effect of NICE's proposed recommendations, which is to limit treatment for malignant pleural mesothelioma to products which are untested and unlicensed for this indication is perverse</u>

Pemetrexed disodium is the only treatment with proven efficacy against malignant pleural mesothelioma, as demonstrated in high quality randomised controlled trials, licensed in the UK.

The other agents used in the UK to treat patients with this condition are unlicensed and, as recognised by the Assessment Group, the evidence base for their efficacy is small and inconclusive. LRiG concluded that there was no objective basis on which to estimate the survival gains of MVP and vinorelbine. Malignant pleural mesothelioma is a rare condition and the manufacturers of the alternative agents have no intention to conduct high quality trials to test the

effectiveness of such products in its treatment or to seek an authorisation in respect of this indication.

In these circumstances, the effect of NICE's proposed recommendations is that vulnerable patients suffering from a devastating and rare disease will be deprived of the only medication with proven efficacy in this indication and limited to symptom control only or to treatment with medicines which have no demonstrated benefit. The failure by the Appraisal Committee to consider the absence of evidence in relation to the effects of alternative therapies and the effects of its recommendations is perverse.

4.2 The statement that it is uncertain whether chemotherapy offers any benefits over ASC/BSC in terms of survival and quality of life is inconsistent with the trial data for pemetrexed disodium

At paragraph 2.7 of the FAD, the Appraisal Committee expresses the view that it is uncertain whether chemotherapy offers any benefits in terms of survival and quality of life. However the EMPHACIS trial which formed the basis of the authorisations granted to pemetrexed disodium, found that, while all patients received best supportive care/ active symptom control, the addition of pemetrexed resulted in a significant increase in both survival and quality of life in patients who received treatment.

In addition, pemetrexed/cisplatin is recognised as the standard of care in malignant pleural mesothelioma in Europe and the USA, and is now the comparator against which new therapies will need to be judged.

In these circumstances, the statement by the Appraisal Committee at paragraph 2.7 of the FAD is inconsistent with the available data and therefore perverse. It is moreover, an attempt to contradict the conclusions of the regulatory authorities and, to that extent, also represents an excess of NICE's powers under Ground 3.

4.3 The restriction of treatment to the clinical trial context is perverse.

The effect of NICE's proposed determination is that patients with malignant pleural mesothelioma in England and Wales will be unable to receive any licensed treatment for their condition, unless they agree to participate in a randomised controlled trial. (The only alternative, is to receive unlicensed and untested treatment as part of "standard care".) Lilly believes that the resulting pressure placed on patients to participate in the proposed trials would be enormous and wholly unethical. It is therefore perverse.

5. *Ground 3: the institute has exceeded its powers.*

5.1 The proposed recommendations have the effect of acting as an unlawful restriction on the prescription of pemetrexed disodium

Directive 89/105/EEC (the Transparency Directive) provides that measures which restrict the range of medicinal products covered by the health system of a Member State, must comply with the terms of the Directive.

The Transparency Directive requires the UK government to notify to the European Commission a series of criteria which are used to determine whether products are excluded from the scope of the NHS in the UK. The UK government has notified a series criteria which it will use for this purpose; these criteria do not include clinical and cost effectiveness.

NICE's appraisals constitute measures within the scope of the Directive, because they lead to a de facto restriction on the prescription of medicinal products within the NHS in England and Wales.

The fact that the Institute's determinations are characterised as "guidance" is immaterial because of the measures contributed to by NICE, which provide penalties for the failure to adhere to the Institute's decisions. Section 5 of the FAD with respect to pemetrexed disodium confirms that, in England, the Healthcare Commission will assess the performance of NHS organisations in meeting core and developmental standards. Those standards were set by the Department of Health together with NICE and in its publication "Standards for Better Health", issued in July 2004, one of the core standards is compliance with NICE's determinations. The position is similar in Wales. Furthermore, the Department of Health Direction of December 2001, which makes funding for technologies recommended by NICE mandatory, has the effect that, where a treatment such as pemetrexed disodium is not so recommended, funding will not be made available.

Therefore, a determination by NICE that pemetrexed disodium should not be recommended for NHS treatment with patients in England and Wales with malignant pleural mesothelioma on the basis that *"there was insufficient evidence to demonstrate that pemetrexed disodium plus cisplatin was superior to other, far less costly treatment regimens and was not persuaded that it was cost effective in the treatment of MPM"* is unlawful and a matter of Community law, because it restricts the use of the product, based on criteria that have not been notified to the European Commission.

5.2 NICE's reliance on the fact that the results of the MS01 study will be published in 2007 is outside the scope of this appraisal

In formulating its conclusions in the FAD, NICE places substantial weight on the fact that the MS01 Study is being conducted, investigating the effects of alternative treatments and best supportive care for patients with malignant pleural mesothelioma, in the context of the inadequate evidence base for such therapies.

However, NICE is required to base its decision on the best available evidence and may not refuse NHS use of pemetrexed disodium on the basis (even if this is only part of the reason) that there is no alternative standard treatment, the evidence for alternatives is poor and that a further study is expected to report in the medium term. Such an approach represents an excess of powers by the Institute.

Moreover, the statements in the FAD at paragraphs 4.3.3 suggest that the Appraisal Committee may have been concerned that a positive recommendation for pemetrexed disodium would prejudice the MS01 Study and were influenced by this in reaching their conclusions. Again such a factor is not a proper basis for any determination by NICE and any influence exerted as a result of such concerns would also represent an excess of powers by the Institute.

5.3 NICE's proposed determination is inconsistent with the stated policy of the European Union to encourage innovation of medicinal products to treat rare conditions

The European Union, fully supported by the UK Government, has taken the view that patients suffering from rare diseases should have the same access to effective treatments as patients suffering from diseases that are more common. As a result, incentives have been developed to encourage companies to invest in the research and development of products to treat such rare conditions, with the view that such medicines should urgently be made available to patients in Europe. The approach by NICE in the context of this appraisal is therefore inconsistent with Community policy.

While pemetrexed disodium is not designated as an orphan drug for the treatment of malignant pleural mesothelioma (based on the fact that an application was made for authorisations in two

indications), the disease clearly falls within the orphan definition. However, the Appraisal Committee has failed to grasp and make clear its policy in relation to judging the cost effectiveness for the treatments for such diseases, which, by their nature, will be expensive. NICE's failure to make clear how it proposes to adjust its appraisal of cost effectiveness to take account of the particular situation of patients suffering from orphan diseases is very unsatisfactory. This is particularly so when the product in question is for a form of cancer and that disease is, according to the Secretary of State's directions, meant to be given a priority by NICE.

The absence of any real consideration having been given to the particular status of orphan diseases is the more surprising given the fact that NICE has stated that it is sympathetic to the longer term interests of the NHS in encouraging innovations of benefit to patients. It is respectfully suggested that NICE, in fact, is doing in this appraisal precisely what was said by the NHS Executive it would never do, namely:

"Placing disproportionate burdens on those who are developing clinical innovations for use in the NHS or risking delay in the effective introduction of those innovations offering worthwhile benefits to patients".

6. *Requested actions*

Lilly therefore respectfully requests that the Appeal Panel should refer this appraisal back to the Appraisal Committee for further consideration with the following Directions:

- That the full evidence base relied upon by the Appraisal Committee in formulating its conclusions should be disclosed to consultees.
- That the reasoning of the Appraisal Committee should be clarified to allow consultees to understand the rationale behind the conclusions set out in the FAD.
- That the Appraisal Committee should consider the approach followed in other appraisals where a clear clinical benefit was obtained by patients suffering a rare and fatal disease, and where the provision of treatment is associated with limited overall cost consequences for the NHS.
- The Appraisal Committee should explain why pemetrexed disodium does not meet the additional criteria laid out in NICE's procedure for accepting treatments above £30,000 cost/QALY.

Yours sincerely

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