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Dear Mr Feinmann

**Re: Response to the NICE Appraisal Consultation Document on Pemetrexed in Non-Small Cell Lung Cancer**

Lilly appreciates the opportunity to comment on the evidence base used to inform NICE's preliminary decision regarding pemetrexed (Alimta®) for use as a second-line treatment in patients with non-small cell lung cancer (NSCLC) in England and Wales.

The basis of NICE's preliminary decision not to recommend pemetrexed is focused around concerns raised by the Liverpool Review Group (ERG) regarding the economic case presented in the Lilly submission. The aim of this response document is to objectively address these concerns drawing on the published evidence and guidelines regarding methodological best practice in health services research and economic evaluation. We have structured our response to include a summary of the key points (section 1) and a detailed analysis of the ERG report (section 2). In preparing our response we have also reviewed the evidence on the erlotinib appraisal and have highlighted inconsistencies in the approach adopted by the ERG to the pemetrexed review to that of the erlotinib review. We have also prepared a separate response to the erlotinib single technology appraisal under the STA process.

We hope that the Appraisal Committee will reconsider their decision on the basis of the following points regarding the appraisal.

## SECTION 1 – SUMMARY OF KEY POINTS

***Clinical positioning and benefits of pemetrexed in NSCLC***

In the Lilly submission, pemetrexed was clearly positioned, not as a substitute for docetaxel as standard of care in second-line NSCLC, but as an **alternative option** to docetaxel in the following circumstances, where Best Supportive Care (BSC) would be conventional therapy:

1) if the patient has received a taxane (docetaxel or paclitaxel) as their first-line treatment and cannot be re-exposed to docetaxel (approximately 20% of first-line NSCLC patients, UK market research data)
2) if the patient is allergic to or unable to tolerate docetaxel and yet is suitable for active chemotherapy; and/or

3) if the physician and/or patient has significant concerns regarding toxicity associated with docetaxel.

It is for these reasons, and, notably, at the request of NICE when defining the decision problem, that Lilly included an unadjusted (pooled) and adjusted (anchored using hazard ratios) indirect comparison to BSC in the submission. The Lilly submission on pemetrexed presented an economic model to the ERG that allowed them to perform either adjusted or unadjusted indirect comparisons, in keeping with the agreed scope of the NICE Decision Problem; that being to compare pemetrexed against docetaxel, erlotinib and best supportive care.

There is a strong clinical case to support the use of pemetrexed:

- Pemetrexed is the first single-agent therapy that has been licensed for second-line therapy in patients with advanced NSCLC based on a Phase III RCT (JMEI) that used docetaxel as a comparator. The trial results are based on 541 patients (265 patients on the pemetrexed arm, and 276 patients on docetaxel). In this study, pemetrexed and docetaxel achieve comparable survival and marketing authorisation was given on this basis in 79 countries worldwide. Docetaxel is recommended by NICE and recognised by regulators as providing significant survival benefit over BSC; therefore, it can be assumed pemetrexed also provides benefit over BSC.

- Febrile neutropenia is associated with a mortality of 9.5% in hospitalised cases (Kuderer et al, 2006). In the JMEI trial 1 in 8 patients who receive docetaxel, compared to 1 in 55 patients who receive pemetrexed, experienced febrile neutropenia. This is a significant reduction in risk for patients with advanced cancer treated with pemetrexed. Significantly fewer patients treated with pemetrexed in the JMEI trial were hospitalised due to febrile neutropenia than those treated with docetaxel (2% vs 13%); likewise, significantly fewer patients treated with pemetrexed- required G-CSF support (3% vs 19%).

- There are additional severe and life-threatening toxicities associated with docetaxel which require hospitalisation, such as grade 3/4 diarrhoea and vomiting. It is unfortunate that the Appraisal Consultation Document (ACD) and ERG documents undermine the significance of patients to experiencing severe treatment related side-effects associated with docetaxel as these have a significant impact on the well being of the NSCLC patient.

- Pemetrexed costs £640-800 per cycle more than docetaxel for a mean of 4 cycles, a total cost increase of around £3000 per treated patient. The cost of managing one episode of febrile neutropenia is quoted as £3582 by both Lilly in the current submission, Roche in the erlotinib submission and Aventis in the original submission for docetaxel.

The ERG has over-emphasised the comparison of pemetrexed to docetaxel, has rejected the unadjusted economic comparison and yet failed to utilise the adjusted indirect comparison that was provided. It is of note that the economic case for erlotinib described in the Roche submission also employed an unadjusted method of indirect comparison alone to compare erlotinib to docetaxel and yet the ERG has not rejected this analysis.

The presentation of extreme cost per QALY results by the ERG (particularly in a situation of comparable efficacy where cost per QALY estimates tend to be unstable and sensitive to very small changes in outcome) is not conducive to evidence-based pragmatic decision-making in the NHS, does not support the balanced appraisal of clinical benefit by the appraisal committee and finally, fails to adequately represent the patients' or physicians' perspective in treating a terminal disease where the palliation is the key aim of treatment.

***Economic assessment of pemetrexed***

Below is a summary of the extreme or inaccurate values used in the ERG calculations which have led to such discrepancy in the incremental cost per QALYs quoted in the Lilly submission and the ACD. Full detailed analysis of these points is given in section 2.

- The mean number of cycles used by the ERG to estimate the treatment cost of pemetrexed in the ACD was 5 (page 3). However the mean number of cycles administered in the JMEI trial was 3.9 for docetaxel and 4.4 for pemetrexed (no significant difference), the median was 4 cycles for each arm. The model provided by Lilly demonstrated an average use of 3 cycles per patient, based upon treatment until progression or discontinuation. This reflects expected UK practice and, as such, is supported on page 20 of the ERG report. The pivotal impact of the duration of therapy on the cost per QALY is highlighted by the ERG in their report.

- The ERG has assigned a body surface area (BSA) that is too high for advanced lung cancer patients. The average body surface area used by Lilly was $1.7m^2$. This was based on a large naturalistic study of first-line NSCLC patients in the UK (n=197) which showed the average BSA was $1.80m^2$ (Bischoff 2005). It is perfectly legitimate to assume that patients receiving second-line treatment for NSCLC are thinner than those at first-line, as the patient loses weight over the course of the illness. This assumption was endorsed by UK clinical experts and pharmacists. It is of note that the ERG used a BSA of $1.83m^2$ based upon Australian, not UK, patients who suffered from a variety of cancer types, including prostate and breast cancers. The use of a mean of 1.83 $m^2$ BSA by the ERG has a critical impact upon the cost per QALY estimate as it leads to the use of a third vial of pemetrexed each cycle – this would not happen in UK clinical practice as the dose would not be increased beyond a BSA of $2.0m^2$, i.e. 2 x 500mg vials, 1000mg of pemetrexed per cycle. The ERG estimates a mean cost of £1768.55 per cycle based on 2.2 vials use per patient, whereas treatment of a patient with a maximum BSA of $2.0m^2$ would cost of only £1600 per cycle (£800 per vial).

- It is not appropriate to apply the same or greater BSC costs to an active chemotherapy arm when comparing pemetrexed to BSC alone. BSC is not used to the same degree in clinical trial populations as active therapy significantly reduces the symptoms that make BSC necessary. There were no differences in symptom benefit between docetaxel and pemetrexed because reduction in key symptoms, including dyspnoea, haemoptysis (bloody cough) and pain were comparable between both therapies. These are the symptoms that would require BSC. It is of note that BSC costs were not applied by the ERG to the erlotinib or docetaxel arm in the current STA or to the docetaxel arm in the previous NICE appraisal for second-line NSCLC. The impact of excluding BSC costs in the active pemetrexed arm is to reduce the incremental cost per QALY for pemetrexed compared with BSC to £44,993, from £59,431 in the ERG calculations, without any other changes to the effectiveness estimates used by ERG.

- The comparison of pemetrexed to BSC by the ERG was not based upon the pemetrexed mean survival from the JMEI clinical trial. It is inaccurate to assume a survival benefit of only 1.62 months for pemetrexed compared to BSC (8.76 vs 7.16 months, as in the ERG estimates) when the median survival in the trial was 8.3 months and can be compared to a median of 4.7 months for BSC (Shepherd et al., 2000). Based upon the difference in median survival alone, which is likely to under-estimate the true survival benefit, the incremental cost per QALY would be £23,006 for pemetrexed compared to BSC, assuming a BSA of $1.75m^2$.

- It is not appropriate to deny the utility benefits of avoiding toxicity through use of pemetrexed, but these were reduced ten-fold to almost zero by the ERG on the basis that the trial had not demonstrated a difference in health-related quality of life (QoL) and efficacy between docetaxel and pemetrexed. There are two reasons why there was no significant difference in QOL between docetaxel and pemetrexed despite the significant reduction in severe toxicities: 1) The Lung Cancer Symptom Scale (LCSS) measures disease

**symptoms** and does not include any assessment of side effects – therefore it does not measure how drug-related toxicity impacts on the patient's QoL. 2) Patients suffering from grade 3 or 4 toxicity do not complete QoL questionnaires so it is difficult to assess the QoL impact of toxicity. The LCSS, in this case, was only administered when patients received treatment, not when they suffered a toxic event. To undermine the utility (QoL) benefit of avoiding life-threatening toxicities goes against all clinical beliefs in the treatment of cancer patients and, in the assessment of two medicines with otherwise comparable efficacy, small differences in utility are known to have a disproportionately large impact on the incremental cost per QALY.

- It should be noted that while toxicity-related QoL was not collected in the JMEI trial there is evidence to suggest a toxicity-related QoL benefit with pemetrexed is expected. During an exploratory analysis of JMEI, patients receiving pemetrexed spent significantly longer not experiencing any drug-related blood-toxicity at all compared to docetaxel (mean time: 69.7 days vs 42.3 days), (Bhalla et al 2005). It is reasonable to assume that if patients receiving pemetrexed are spending significantly longer without toxicity this would be translated to a QoL benefit to the patient.

## SECTION 2 – DETAILED ANALYSIS OF THE ACD AND ERG APPRAISAL OF PEMETREXED

### Section 2.1. Clinical Analysis

#### *2.1.1 Efficacy of Pemetrexed vs. Docetaxel*

The efficacy of pemetrexed, based on JMEI, has been called into question by the ERG. Lilly wishes to point out that results from JMEI has been the basis of regulatory approval for pemetrexed in 79 countries worldwide including the European Union and USA on the basis of comparable efficacy to docetaxel.

Pemetrexed was granted license by the European Medicines Agency (EMEA) in 2004 for the treatment of patients with second-line NSCLC. The evidence presented to the EMEA included the phase III randomised clinical trial of pemetrexed compared to docetaxel (JMEI). The EMEA EPAR in relation to JMEI states that '...although non-inferiority was not formally demonstrated, the data submitted are robust enough to conclude that a clinically significant inferiority of pemetrexed to docetaxel in terms of efficacy in this population is unlikely". The EMEA go on to state that any possible differences in efficacy between pemetrexed and docetaxel are likely to be marginal. Overall, the benefit/risk ratio of pemetrexed compared to docetaxel puts the two products on the same line given the fact that the efficacy can be considered as similar. The benefit/risk ratio of pemetrexed as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy was favourable, and therefore recommended the granting of the marketing authorisation (EPAR, 2004).

The ERG report [page 25 of 58] discusses a statistical review of JMEI trial undertaken by the FDA quoting the following statement by the FDA "…the study [JMEI] failed to demonstrate superior efficacy as per the trial protocol…failed to demonstrate efficacy based on the fixed margin non-inferiority test as defined in the amended protocol…[and] based on the FDA analysis the study failed to demonstrate efficacy based on the percent retention of control effect non-inferiority testing". In response to these statements, Lilly would refer the ERG back to the FDA and take note of the following statements from the FDA drug approval summary (Cohen et al, 2005) to provide context to the ERG comments:

On Aug 19, 2004, Food and Drug Administration (FDA) granted pemetrexed an accelerated approval as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC who had received prior chemotherapy (Cohen et al, 2005). The accelerated approval was based on the tumour response and the favourable safety profile seen with pemetrexed in the JMEI study. The medical review of the approval signed by Director of the FDA is available on the FDA website.

An updated analysis on the survival data has recently been published. This reflects data available 23 months after the original analysis and after 519 deaths in the study population. These updated survival analyses consistently show that second-line pemetrexed has comparable survival to docetaxel in patients with NSCLC (Demarinis et al, 2006).

### *2.1.2 Side effect profile of Pemetrexed vs. Docetaxel*

The ACD has overlooked the data related to the significant benefits associated with the use of pemetrexed in the setting described, in terms of haematologic and non-haematologic toxicities.

According to the FDA drug summary (Cohen et al, 2005) pemetrexed was felt to have a more favourable safety profile than docetaxel. Of greatest importance pemetrexed caused significantly less neutropenia, neutropenic infections, and need for granulocyte/macrophage colony-stimulating factors. The following are some significant toxicity results from the JMEI trial (Hanna et al, 2004)

- Patients treated with pemetrexed had significantly less grade 3/4 neutropenia (5 vs 40%), p<0.001
- Less febrile neutropenia (2 vs 13%) with pemetrexed compared to docetaxel, p<0.001
- Less infection with grade 3/4 neutropenia (0 vs 3%) than those treated with docetaxel, p=0.004
- Significantly fewer patients treated with pemetrexed were hospitalised due to febrile neutropenia than those treated with docetaxel (2 vs 13%), p<0.001
- Significantly fewer patients treated with pemetrexed- required G-CSF support (3 vs 19%), p<0.001

Lilly wish to draw attention to two exploratory analyses which further support the FDA statements regarding the favourable safety profile of pemetrexed. In the first, Pujol et al (2005) looked at how long patients survived without experiencing any grade 3/4 toxicities (severe toxicities, most often requiring hospitalisation). The results demonstrated a statistically significant longer toxicity-free survival time for pemetrexed compared with docetaxel. This is clearly a significant benefit for this group of patients.

| | **Pemetrexed (n=265)** | **Docetaxel (n=276)** |
|---|---|---|
| Median Survival Time | 1.2 months | 0.4 months |
| Hazard Ratio | 0.6 | |
| 95% CI for HR | (0.50–0.72) | |
| p-value | <.0001 | |
| 1-year Toxicity-Free Survival | 12.20% | 6.10% |

In another exploratory analysis of JMEI looking at burden that drug-related toxicities have on patients, Bhalla et al (2005) found that patients receiving pemetrexed spent significantly longer not experiencing any drug-related toxicity (grade 1-4) at all compared to docetaxel. The differences are more pronounced with high grade toxicities which are considered severe and life-threatening. It is reasonable to assume that if patients receiving pemetrexed are spending significantly longer without drug-related toxicity this would be translated to a QoL benefit to the patient.

**Toxicity burden to be borne by the average patient in JMEI (Bhalla, 2005)**

| | Mean time (days) | | |
|---|---|---|---|
| | Docetaxel | Pemetrexed | |
| | 238 patients | 212 patients | P-value |
| Haematological toxicity grade | | | |
| Time spent receiving chemotherapy | 77.9 | 88.8 | 0.278 |
| Time with no drug-related toxicity | 42.3 | 69.7 | <0.001 |
| Time with toxicity Grade 1 | 5.2 | 7.6 | 0.688 |
| Time with toxicity Grade 2 | 5.5 | 8.5 | 0.587 |
| Time with toxicity Grade 3 | 10 | 2.1 | <0.001 |
| Time with toxicity Grade 4 | 14.9 | 0.9 | <0.001 |
| Non-Haematological toxicity grade | | | |
| Time with no drug-related toxicity | 16.4 | 22.8 | 0.04 |
| Time with toxicity Grade 1 | 21.6 | 32.9 | 0.027 |
| Time with toxicity Grade 2 | 28.3 | 28.3 | 0.39 |
| Time with toxicity Grade 3 | 10.3 | 4.6 | 0.001 |
| Time with toxicity Grade 4 | 1.2 | 0.3 | 0.02 |

Section 4.4 of the ACD discusses that only patients who experience allergic reactions to docetaxel would be considered for pemetrexed. Based on a survey including over 70 clinical oncologists, medical oncologists and chest physicians, 82% stated that docetaxel has treatment limiting side-effects (Lilly Data on File, 2006).

Lastly, the reason some patients are not suitable for docetaxel is the high incidence of grade 3/4 toxicities. With respect to treatment of non-haematological toxicities such as nausea, vomiting and diarrhoea, patients need IV fluids, parenteral nutrition, and in some cases patients need to be admitted to an intensive care unit (see Chemotherapy Pathway Document obtained from local Hampshire hospital, Appendix 1). Severe alopecia (severe and total hair loss), however is irreversible.

The impact of toxicities on the patients QoL should not be underestimated given palliative aim of treatment in advance lung cancer.

## Section 2.2. Economic Analysis

### *2.2.1 The Method of Indirect Comparison*

The Evidence Review Group Report (ERGR) on pemetrexed on page 8 [of 58] states '***the methods used to perform the indirect comparison were considered by the evidence review group to be inappropriate. The results obtained by the methods employed cannot be considered reliable or meaningful, since they effectively undermine all of the benefits of randomization inherent in the source trials and do not adjust for the resulting imbalances between the pooled comparators. The only direct and reliable clinical evidence available, which is relevant to the reference case of this appraisal, is therefore the JMEI trial of pemetrexed versus docetaxel'.***

It is important that the terminology used here is sufficiently defined. Use of the generic term 'indirect' comparison needs to be further disaggregated, in order to better understand the nature of the ERG concerns. Indirect comparisons present in two forms - adjusted and unadjusted. An **adjusted indirect comparison** is a comparison of a single treatment that is adjusted by the results of a direct comparison with a common control group, partially using the strength of the RCT. Adjusted indirect comparisons can only be performed where there is a common treatment that links one clinical trial to another, such as a placebo. An **unadjusted indirect comparison** is the term given to an analysis where data on the absolute values are pooled across treatment arms or taken as single estimates. This latter form of treatment comparison is typically reserved for situations where an adjusted indirect comparison is not permissible, due to the absence of trials that provide linkages between treatments, such as in the recent case of the NICE submission on gemcitabine as a treatment for metastatic breast cancer.

The Lilly submission on pemetrexed presented an economic model to the ERG that allowed users (of the model) to perform either form of indirect comparison (adjusted or unadjusted) in keeping with the agreed scope of the NICE Decision Problem; that being to compare pemetrexed against docetaxel, erlotinib and BSC. A direct comparison, on the other hand, using data from a head-to-head comparison of pemetrexed versus docetaxel in the JMEI trial, as advised by the ERG, would have failed to incorporate two of the comparator arms in the agreed Decision Problem, BSC and erlotinib, as well as four additional phase III RCTs available on docetaxel.

The ERG did not adhere to the scope of the agreed Decision Problem when reviewing the Lilly submission on pemetrexed. They neither made it known within their evidence review report that the cost-effectiveness of pemetrexed had in fact been determined using both methods of indirect comparison. The ERG claimed that the methods employed were inappropriate, despite the Decision Problem agreed by NICE prior to the Lilly submission clearly stating the need to compare pemetrexed to other second-line treatments that included BSC as well as docetaxel and erlotinib. The methods adopted by Lilly were thus entirely justified and appropriate for the Decision Problem in question.

Page 29 [of 58] of the ERGR on pemetrexed contains the statements '***the company submission does refer to the Bucher indirect method but the method has not been applied correctly since treatment arm level data have been used instead of (log) hazard ratio estimates' and 'the company submission does not use an adjusted indirect comparison***'. Not only does the economic model permit both types of indirect comparison (as explained above) but the results of the adjusted indirect comparison are presented in the sensitivity analyses in the submission document.

The economic case for erlotinib described in the submission by Roche focused on a comparison against docetaxel (their chosen comparator) that employed an **unadjusted** method of indirect comparison alone. The opportunity did exist to perform an **adjusted** indirect comparison using data on erlotinib from the BR21 trial (Shepherd et al., 2005) and data from the randomised controlled trial of docetaxel vs. BSC reported by Shepherd et al., (2000) - using the BSC arm as the treatment linking the two treatments to one another. Therefore, Lilly find it surprising that there is no mention in the ERG report on erlotinib on the importance and appropriateness of using the Shepherd et al., (2000) trial to link erlotinib to docetaxel using BSC as the treatment link despite the Shepherd et al., (2000) trial being a pivotal phase III clinical trial in the published evidence base for docetaxel.

### *2.2.2 Flaws in the adjustments made by the ERG and the resultant ICERs*

The ERG having questioned the efficacy of pemetrexed vs. docetaxel based on the head-to-head JMEI trial, re-calculated a cost per QALY for pemetrexed compared to docetaxel by substituting existing values for overall survival contained within the economic model with the absolute values for overall median survival for docetaxel reported in the JMEI trial. In doing so, the ERG make the assumption that pemetrexed achieves the same overall survival as docetaxel (which is 34.23 weeks). The ERG reported a cost per QALY of £458,333. However, when the same task was repeated by Lilly, the cost per QALY produced was £164,956

In addition to modifying the estimates for overall survival in an attempt to replicate the cost of £1,129,123 per QALY reported in the ERGR on pemetrexed, the Lilly Health Outcomes Team further changed the following variables in their model:

- Time to disease progression for pemetrexed to equate to the same as docetaxel (using data reported in the JMEI trial)
- Overall response rates for pemetrexed to equate to the same as docetaxel (using data reported in the JMEI trial)
- Adverse events rates to reflect the profile for each product as observed in the JMEI trial
- Treatment discontinuation rates due to adverse events to reflect the same in the JMEI trial for docetaxel; and
- Employed a half-cycle correction in the model for the adverse events.

Introducing these changes increased the cost per QALY for pemetrexed compared to docetaxel to £243,609.

Further changes to the assumptions of the model that included the following, made very little difference to the above cost per QALY, although the justification for questioning the original assumptions employed in the model cannot be reliably substantiated.

- Changing the body surface area used to perform the chemotherapy drug calculations from $1.7m^2$ to $1.83m^2$;
- Changing the maximum number of chemotherapy cycles in the model, despite the fact that the median number of cycles within the economic model was 4;
- Using per vial as opposed to per mg costing;
- Changing the unit cost of febrile neutropenia to £2,257.50;
- Assuming 10.6% of patients receiving pemetrexed require an in-patient stay and 13.9% of patients receiving docetaxel the same;
- Assuming admitted patients have 2 journeys per cycle from the hospital to the chemotherapy centre for pemetrexed and docetaxel.

These high costs per QALY assume clinical equivalence however which is not a valid assumption based on the clinical trial evidence of JMEI.

The ERG report on page 44 [of 58] states that the overall utility gains were also re-estimated for pemetrexed over docetaxel to produce their cost per QALY of £458,333, however it is not clear how these calculations were performed. When Lilly requested clarification from NICE so that they too could replicate this analysis, the response dated 15th November 2006 was 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***'.

Further, there is a lack of transparency on how the ERG has applied their adjustments to the number of treatment cycles with pemetrexed and docetaxel. The model provided by Lilly is based on a maximum of 6 cycles (as most patients in clinical practice receive up to 4 cycles of chemotherapy). In the JMEI trial, 96.7% of patients treated with pemetrexed had responded (complete or partial

response) by cycle 6 and less than 20% of patients on pemetrexed continued to receive chemotherapy beyond cycle 6.

Lilly were therefore unable to reliably determine due to the lack of transparency in the ERG methods how the cost of £1,129,123 per QALY calculation had been performed. It is most unlikely that this cost was estimated using the Lilly economic model correctly.

#### *2.2.3 Acquisition cost of pemetrexed*

The acquisition cost of pemetrexed in section 2.4 of the ACD is listed as £8000 for a typical course of treatment. A typical course of treatment will range between 3-4 cycles of pemetrexed which equates to £4,800-£6,400. This cost assumes vial wastage and is based on varying body surface area for patients.

#### *2.2.4 Coverage of databases employed in the systematic literature review*

Lilly undertook a systematic review of the literature in order to identify relevant phase III clinical trials for use in their Lilly submission on pemetrexed, which fulfilled the NICE STA requirements. The ERG criticise the review in claiming [page 18 of 58] that '***other relevant databases and conference sites were not searched such as the Web of Science, ISI Proceedings and the European Society for Medical Oncology (ESMO) proceedings***'. In addition to adhering to the NICE STA requirements, Lilly consulted the health technology assessment (HTA) report by Royle & Waugh (2003) entitled '*Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system'* which clearly state that '*searching additional databases beyond the Cochrane Library (which includes CCTR, NHS EED and the HTA database), MEDLINE, EMBASE and SCI, plus BIOSIS limited to meeting abstracts only, is seldom effective in retrieving additional studies for inclusion in the clinical and cost-effectiveness sections of TARs (apart from reviews of cancer therapies, where a search of the ASCO database is recommended). A more selective approach to database searching would suffice in most cases*'. The coverage of databases employed in the Lilly submission on pemetrexed can thus unequivocally be deemed complete and appropriate.

#### *2.2.5 Methods employed with respect to the reporting of data from the systematic review of the economic evidence*

The ERGR [page 33 of 58] claims that '***data were extracted on title, aims and methods, results and relevance to decision-making in England and Wales. Both forms of data extraction are simplistic and do not provide sufficient details for a comprehensive comparison of studies***'.

Lilly are concerned that the ERG were not familiar with the requirements of the NICE STA form under Section 3.1.2 entitled 'Description of Identified Studies' that asks manufacturers to 'provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales'. Nevertheless, Lilly believe they have completed the STA form as stipulated by NICE and hope the ERG will recognise this part of the NICE STA form requirement.

#### *2.2.6 Trial Characteristics*

Page 21 [of 67] of the ERGR on pemetrexed refers to the pivotal clinical trial of pemetrexed and states that '***the mean number of patients per site is 4 (125 centres from 23 countries). Such contextual diversity and small numbers may undermine some of the benefits of randomization, and also cast doubt on the applicability of results to any one country***'.

Assessment of the external validity of data obtained from randomized controlled trials is a well documented problem. Nevertheless, this form of scientific evidence represents the highest quality for use in clinical evaluations. There is no evidence to support the notion that the results of the JMEI trial cannot be generalised to the UK. Accepting the ERG's argument implies that all data obtained from multi-centre, multinational RCTs are redundant by virtue of the fact that none of the results apply to any one country, which is not realistic.

### *2.2.7 Critique of the Lilly Company Model*

Lilly developed a multi-state transitory Markov model to perform the economic evaluation of pemetrexed compared to relevant comparator therapies in the second-line treatment setting. This model incorporated the effect of treatment on overall survival, time to disease progression and importantly, the effect of a wide range of adverse events using utility values obtained from the largest and most comprehensive study performed to date in NSCLC. Expert clinical opinion was sought throughout the evaluation to guide the design of the model, the underlying structural assumptions and the configuration of treatment algorithms used for both the administration of chemotherapy and treatment of serious adverse events. The model reflected all of the important costs and clinically meaningful outcomes associated with the disease and its treatment. As such, it scored very highly against common check-lists for economic evaluation methods and adhered to the framework for good practice in modelling proposed by Philips et al., (2004). The design of this model has been successfully employed in metastatic breast cancer and is the most sophisticated model to date produced for evaluating treatments in NSCLC.

The ERGR [page 34 of 58] make the following statements:

- ***Side effects in the company model appear to be restricted to treatment-related events only***.

Side-effects are dealt with in the Lilly submission as treatment-related adverse events, not disease symptoms. Lilly are interested to understand what the ERG would consider to be side-effects of the different treatments that are not, as they describe, treatment-related.

- ***Death only occurs in the progressive health state or for patients experiencing febrile neutropenia.***

Lilly fail to see the rationale for over-complicating the model by introducing random events such as deaths not occurring as a result of disease progression or serious adverse events. These two causes of death are the two most likely causes amongst this patient population, which is the reason why they have been used in the model.

- ***The model does not allow for patients to die of anything other than cancer, or treatment-related causes, which is an unrealistic assumption.***

If the economic model was to allow for patients to die of anything other than cancer or treatment-related causes, then it would be impossible to reliably determine which of the treatments under evaluation were the most effective or cost-effective. Inclusion of data of this sort would bias against treatments where, for example, patients were involved in road traffic accidents. It is not appropriate or reasonable to introduce this kind of 'noise' into the model.

- ***Drug administration costs***

The ERG criticise Lilly for not employing the full daily cost of chemotherapy administration in the model for each treatment, despite the fact that patients spend variable amounts of time receiving their treatment because of differences in the administration times between docetaxel and pemetrexed. The differences in administration times are not irrelevant on the grounds that hospitals are reimbursed for their costs according to a reference or tariff cost so such differences do matter. Hospitals are still required to make use of treatment pathways to avoid bottle-necks in the system and opt for cost-minimizing practices where appropriate. The economic model produced by Lilly uses the tariff as a basis for estimating hourly costs of treatment but does allow for differences in administration times. There is no evidence to support the ERG assumption that patients require transportation to and from hospital to a chemotherapy centre to receive treatment and furthermore does not differentiate between docetaxel or pemetrexed.

***Cost estimates for febrile neutropenia***

The ERG substitute the published cost estimate for febrile neutropenia contained within the economic model with their own cost estimate that they calculate using an un-validated treatment algorithm

populated with unit costs that are at least two years out of date. It is thus not surprising that the resultant cost would be lower than that used in the economic model however there are no valid grounds for questioning the accuracy of the original unit cost estimate used. This estimate was included in the Lilly submission, the erlotinib submission and in the original appraisal of docetaxel in second-line NSCLC.

## Section 2.3 Other

### *2.3.1 Approval of pemetrexed by other bodies*

The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia approved pemetrexed for NSCLC in November 2004 and pemetrexed is currently under review by the Scottish Medicines Consortium (SMC). The ERG state [page 14 of 58] '***pemetrexed has not been reviewed by the Scottish Medicines Consortium (SMC) despite the company being asked on several occasions to make a submission. The SMC viewed the company's decision not to submit as a failure to prove their case for pemetrexed and hence the medicine was not recommended for use in Scotland***'.

Lilly can confirm that further to a single request from the SMC, we have made a submission to SMC. The decision not to submit previously was based upon the very low numbers of eligible patients anticipated in Scotland – as was communicated to the SMC by Lilly. In a teleconference with NICE and Lilly earlier this year, Lilly clarified this point with NICE and we are therefore surprised at this statement by the ERG.

## Conclusions

The phase III registration trial (JMEI) demonstrated comparable efficacy between pemetrexed and docetaxel but there were significant safety advantages of pemetrexed over docetaxel including febrile neutropenia and hospitalisation due to febrile neutropenia, and certain severe and life-threatening non-haematologic toxicities such as nausea/vomiting/diarrhoea

With regards to the economic evaluation, we trust that our comments have demonstrated that the estimates produced by the ERG should be viewed with caution because:

- We could not replicate the results produced by the ERG despite incorporating the adjustments the ERG state have been made and;
- The variables and assumptions underpinning the economic model have been subjected by the ERG to the most unlikely range of scenarios and use of alternative input values that neither reflect clinical practice / opinion nor reflect the costs and consequences of the likely implications of the product's use.

In the Lilly submission, pemetrexed was clearly positioned as an alternative option to docetaxel in the following circumstances, where Best Supportive Care would be the current option:

- if the patient has received docetaxel or paclitaxel first-line and cannot be re-exposed to a taxane,
- if the patient is allergic to or unable to tolerate docetaxel and yet is suitable for active chemotherapy
- if the physician and/or patient have significant concerns regarding toxicity associated with docetaxel.

We hope that the Appraisal Committee will reconsider their decision on the basis of the points above and approve pemetrexed as an alternative to docetaxel for patients in whom docetaxel is not suitable.

Yours sincerely

Manager, HTA and Health Outcomes, UK

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## Appendix 1
### Toxicity Definitions and Impact on Patients

| Toxicity (side effects) | Definition | Impact on Patients | Gd 3/4 needs hospitalisation |
|---|---|---|---|
| **Leukopenia** | Reduction in the number of blood cells that fight infection (white blood cells) | Does not cause any symptoms unless the patient comes into contact with an infection, in which case they contract the infection quickly and it may take longer for the infection to resolve. | Sometimes |
| **Neutropenia** | Reduction in the number of blood cells that fight bacterial infection (granulocytes) | | Sometimes |
| **Febrile Neutropenia**[a] | Severe or life threatening neutropenia (grades 3 or 4) with evidence of a raised body temperature. | Indicates the patient has contracted an infection and that the normal body defences are unable to combat it. This is a severe or life threatening condition and thus requires hospitalisation and treatment. | Yes |
| **Anaemia** | Reduction in the number of red cells or haemoglobin level in the blood leading to reduced ability to transport oxygen | People with anaemia can feel tired, fatigue easily, appear pale, develop palpitations, and become short of breath. If anaemia causes symptoms and/or is severe it requires correction by blood transfusion. | Only if transfused as inpatient. |
| **Thrombocytopenia** | Reduction in the number of cells that cause the blood to clot (platelets) | May bruise more easily, cuts may take longer to stop bleeding. If severe spontaneous bleeding may occur (nose bleeds, bleeding from gums, teeth, gut, urinary tract). When severe requires correction by platelet transfusion. | Only if transfused as inpatient. |
| **Nausea**[b] | Feeling of sickness with or without actual vomiting | Severe nausea (grade 3) indicates a patient has no significant oral intake and therefore requires hospitalisation and administration of intravenous fluid. | Yes |
| **Vomiting** | Emesis | Severe (grade 3) vomiting indicates 6 or more episodes in a 24 hour period or the need for hospitalisation and the administration of intravenous fluid. Life threatening (grade 4) vomiting indicates severe metabolic abnormalities requiring intensive care. | Yes |
| **Diarrhoea** | Loose or frequent bowel movements | Severe (grade 3) indicates passing 7 or more stools per day or the need for hospitalisation and administration of intravenous fluids. Life threatening (grade 4) indicates the need for intensive care. | Yes |
| **Stomatitis** | Mouth ulcers | Severe (grade 3) indicates that the patient is unable to swallow and therefore requires assisted hydration and feeding. | Yes |
| **Hand-Foot Syndrome**[b] | The skin on the palms of the hand and soles of the feet becomes dry and flakes off leaving swelling and fissuring | Severe indicates that the condition interferes with function (so the patient has difficulty using the hands and feet) | No |
| **Asthenia** | Muscle weakness | Severe (grade 3) indicates that the condition is interfering with daily living. Grade 4 indicates the patient is bedridden or disabled. | No |
| **Infection** | May occur with or without neutropenia | Severe (grade 3) requires hospitalisation and treatment. Life threatening (grade 4) indicates septicaemia requiring intensive care. | Yes |
| **Motor Neuropathy** | Damage to the nerves that innervate muscles | Severe (grade 3) indicates subjective weakness with impairment of function. Grade 4 indicates paralysis. | No |
| **Sensory Neuropathy**[b] | Damage to the nerves that transmit sensation | Severe indicates sensory loss or pins and needles (parasthesia) that interferes with function. Grade 4 indicates irreversible sensory loss. | No |
| **Peripheral Oedema** | Swelling (due to fluid accumulation) in the dependant parts of the body | Severe indicates swelling that is causing symptoms and is unresponsive to therapy. | Sometimes |
| **Dyspnoea**[c] | Shortness of breath | Severe (grade 3) indicates dyspnoea at a normal level of activity. Grade 4 indicates dyspnoea at rest. | No |

a. Grades 1 and 2 febrile neutropenia do not exist – the grading system starts at "severe" (grade 3)
b. Grade 4 nausea and hand foot syndrome do not exist
c. Grade 1 dyspnoea does not exist – the grading system starts at "moderate" (grade 2)

**Chemotherapy Pathway - Toxicity assessment (Obtained from local Hampshire hospital)**

| Toxicity | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Nausea | None | Able to eat | Oral intake significantly decreased | No significant intake: Requires IV fluids | - |
| Vomiting | None | 1 episode in 24 hrs over pre-treatment | 2-5 episodes in 24 hrs over pre-treatment | 6+ episodes in 24 hrs over pre-treatment, or need for IV fluids | Requires parenteral nutrition or physiologic consequences |
| Diarrhoea | None | Increase of <4 stools/day over pre-treatment | Increase of 4-6 stools//day or nocturnal stools | Increase of 7+ stools/day or incontinence, or need for support for dehydration | Physiologic consequences requiring intensive care |
| Alopecia | None | Minimal | Moderate, patchy. | Complete but reversible | Irreversible |