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Dear Dr Longson

Re: Pemetrexed in the Treatment of Malignant Pleural Mesothelioma

Thank you for forwarding the Appraisal Consultation document (ACD) on pemetrexed and for the opportunity to comment on the Appraisal Committee's preliminary recommendation.

In view of the comments in the ACD that appeared to have shaped the preliminary recommendations regarding pemetrexed in mesothelioma please find below our comments.

The following are a summary of the key points of our response:

- Pemetrexed/cisplatin offers proven survival increase of between 23%-40% compared to cisplatin in a disease for which there are no other proven or licensed treatments.
- If patients respond to pemetrexed, most patients (87%) respond within 4 cycles. The survival gain in responders is significantly better than for non-responders. There is potential to reduce cost by ceasing treatment in patients who have not achieved tumour response within 12 weeks (compared with the 6 cycles in the EMPHACIS study). Increased survival and reduced cost would lead to a lower cost per LY/QALY.
- The incremental cost per Life Year (which emphasises the importance of survival) is only just over £30,000 for patients of good performance status.
- There is no standard care for mesothelioma in the UK. The results of Lilly's model 2 highlight the scarcity of data and therefore inconclusiveness of the evidence base which exists for currently used regimens.
- The MSO-1 trial is not directly relevant to the decision regarding pemetrexed.
- Mesothelioma is an industrial disease estimated to reach peak incidence between the years 2010 and 2015, thereafter declining. Therefore a positive recommendation for pemetrexed could be expected to be a time-limited expenditure for the NHS.
- The innovative nature of this drug, the rare disease and the targeting of treatment to those who benefit most should enable NICE to recommend this therapy.

1. Implementation of clinical guidance in the UK treatment setting

The fully supplemented Stage III/IV advanced disease, good performance status sub-group (FS PS 0/1 Adv) was chosen for the economic analyses for two reasons: 1) it was the group in which patients derived the greatest incremental benefit in terms of survival and QoL and 2) we believed it was the group which reflected patients treated for malignant pleural mesothelioma in the UK.

In the ACD, there is concern that the 'advanced disease' stage III/IV sub-group will not be easily identifiable in routine clinical practice and that in fact chemotherapy is given to patients who are inoperable (inclusion criteria for the JMCH/EMPHACIS trial) and of good performance status.

Therefore the sub-group analysis that we conducted on fully supplemented patients of good performance status (FS PS 0/1) is likely to be more applicable to UK clinical practice. This sub-group of patients demonstrated similar gains in incremental survival and QoL and represented a larger proportion of the trial population (over 75%) compared to the FS PS 0/1 Adv sub-group. This increases the robustness of the results.

The incremental cost per QALY/LY for the FS PS 0/1 group was only slightly higher than that for the PS 0/1 adv disease sub-group.

Table 1: Cost per QALY and LY ratios for FS PS 0/1 and FS PS 0/1 AD patient groups

Patient group (number of patients in both arms)	Mean survival outcomes		Median survival outcomes	
	Incremental cost/LY	Incremental cost/QALY	Incremental cost/LY	Incremental cost/QALY
FS with PS 0/1 (n=284)	£31,688	£48,099	£27,582	£41,596
FS w AD & PS 0/1 (n=207)	£31,337	£47,567	£19,101	£27,824

2. Targeting therapy to optimise clinical and cost-effectiveness in UK clinical practice

In order to support NICE in optimising the clinical and cost-effectiveness of pemetrexed/cisplatin, we have conducted analysis on the impact of cessation of therapy in patients who do not respond to treatment. The tables below show the proportion of responders at each cycle in the clinical trial, and also the survival benefit obtained by responders compared to non-responders.

The cost-effectiveness of pemetrexed/cisplatin was assessed in the submission assuming 6 cycles of therapy (the mean in the clinical trial.) However, in routine clinical practice, not all patients will receive 6 cycles, a clinical decision that is generally made upon the basis of treatment response.

There is a rapid response to pemetrexed treatment, with most patients who are going to achieve tumour response doing so within 4 cycles (87%). The survival gain in responders is also significantly greater than for non-responders. There is, therefore, potential to reduce overall cost by ceasing treatment in patients who have not achieved tumour response within 12 weeks. Increased survival and reduced cost would lead to a lower cost per LY/QALY.

Table 2. Summary of tumour response by cycle, ITT population (N=448).

	Pemetrexed/cisplatin (n=226)		Cisplatin (n=222)	
Cycle	Responders (n)	Cumulative % of responders	Responders (n)	Cumulative % of responders
2	62	66	26	70
3	3	69	2	76
4	17	87	8	97
5	1	88	0	97
6	7	96	1	100
Post-discontinuation	4	100	0	100
Total	94		37	

(A responder was defined as any patient who had a complete response or a partial response -see Appendix 1 for further definition of responder)

It can be seen that among the responders, over half of pem/cis responders (66%) respond by cycle 2 (week 6) and nearly all responders (87%) have done so by cycle 4 (12 weeks). Significantly more pem/cis patients respond to treatment (42%) than cisplatin patients (17%).

Table 3. Survival analysis for responders vs non-responders, 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)		.31	.47
95% CI		(.22-.45)	(.29-.76)

The median survival for pem/cis responders was 18.4 months compared to 14.8 months for cisplatin responders (based on ITT population) whilst non responders did not differ between arms (8.2 vs 8.1 months).

On the basis of this analysis, it is likely that the discontinuation of therapy at 12 weeks, based upon lack of patient response to therapy, will reduce the cost of therapy by at least 2 cycles (£3200), without reducing the survival benefit gained by patients overall.

3. NICE determination of acceptability of therapies for use in the NHS

(i) Cost per QALY versus cost per LYG

While the technology appraisal process guide does make clear NICE's preference for cost-utility analyses, other measures of cost effectiveness are not excluded. However, while it endorses the use of cost–utility analysis in the economic evaluation of particular interventions, cost per LY plays an important part in the assessment of the cost-effectiveness of MPM because this is an end-stage disease and prolonging survival is considered the most important aim of treatment. In addition, it is generally accepted that reliance upon QALYs discriminates against persons with incurable illnesses and those with a short life expectancy. Their use accordingly remains controversial in terms of estimating the value of life gained in terminal diseases.

At the information meeting for consultees it was agreed that a cost per LY analysis would be important analysis to include in the submission. According to NICE's Citizen's Council, there are many instances where it has been necessary to use the 'cost (£) per life year gained or (particularly for anti-cancer drugs) the cost (£) per disease-free life year'. We believe that the Appraisal Committee should have considered the cost per LY analyses as well as the QALY figures before formulating its preliminary determination.

In FS patients of good performance status for example, the range of difference in estimates of cost-effectiveness is **£48,099 per QALY** to **£31,688 per LY** based upon mean survival estimates.

(ii) Mean versus median survival estimates

With survival data containing censored events, it is expected that the mean survival would be biased and would be a poor estimate. In the assessment of oncology medicines, the median is

usually the preferred measure of central tendency for survival data due to the censored events and skewed distribution.

In FS patients of good performance status, the cost-effectiveness estimate range even more greatly when survival is based upon the median rather than the mean, **£41,596 cost per QALY** compared to **£27,582 cost per LY** based upon the median overall survival.

The NICE technology appraisal process guides (published in May 2004) make no specific requirement to use mean over median data. In the past NICE has made recommendations for cancer treatments based on ICERs calculated with median survival data and not mean survival estimates and/or on cost per LY rather than on cost per QALY.

(iii) Cost-effectiveness 'thresholds'

The approach followed by the Appraisal Committee in relation to its consideration of pemetrexed is inconsistent with that followed in other appraisals and is therefore procedurally unfair.

NICE has, in past appraisals, made many oncology recommendations using cost/LY analyses, which is more appropriate in the circumstances of use of these products. It would therefore seem that, to apply a 'maximum acceptable ratio' of £30,000 to pemetrexed in light of the evidence above demonstrates bias against pemetrexed, when the pemetrexed economic case is based on the estimates for the 'worst' case scenario – ie using cost/QALY instead of cost/LY and use of mean vs median survival estimates. The ICER for pemetrexed compared to cisplatin using a median estimate of survival and cost per Life Year gained **is below £30,000 per life year.**

According to NICE, a technology which has an ICER of £30,000/QALY or more requires strong justification on the following factors: degree of uncertainty, innovative nature of the technology, particular features of the condition and the population receiving the technology and finally the wider societal costs and benefits.

Pemetrexed is an innovative medicine for patients with no other licensed therapy available for an industrially caused disease, of (time) limited incidence, which is particularly difficult to treat. It is the only treatment for MPM for which there is a statistically significant benefit in terms of survival and progression free survival demonstrated in randomised controlled trails. The effect of NICE's preliminarily recommendations is to require NHS patients to receive treatment with chemotherapy regiments with no authorisation for this indication and, very little evidence to support the benefits. This is not a fair or rational approach to the treatment of vulnerable patients and is inconsistent with NICE's procedures and the scope for this appraisal.

As pemetrexed currently represents around 40% of chemotherapy treatment given for MPM in the UK, there would be significant clinical and societal implications of withdrawing this treatment from the NHS. Therefore, we believe pemetrexed meets all of the above criteria and, in light of this, NICE should reconsider the use of the maximum ICER acceptability of £30,000 in the appraisal of pemetrexed.

4. Evidence-Based medicine

(i) Current practice in the UK.

Market research for the UK conducted for the submission showed that MVP and vinorelbine were the main chemotherapy regimens used in mesothelioma. The NICE scope also lists these two treatments specifically as comparators. Therefore MVP and vinorelbine are not just 'what the manufacturers consider to be standard of care' (see 4.2.2 in the ACD), they were the most common therapies that were used in the UK *at the time of submission*. However, since the licensed launch of pemetrexed, use of pemetrexed is already estimated to make up around 40% of all chemotherapy used for treatment of MPM. Therefore, current practice is now pemetrexed, MVP and vinorelbine. It is important to note that around half the patients in the UK with MPM do not receive chemotherapy and instead receive Active Symptom Control (ASC), largely due to poor performance status.

Indeed from points 4.3.8 and 5.2 of the ACD, there appears to be inconsistency on what the Appraisal Committee considers as standard treatment for mesothelioma in the UK.

Neither MVP nor vinorelbine are licensed for MPM nor are there plans for the respective manufacturers to seek such a licence. As stated in the TAR and the ACD in reference to Model 2, the evidence base for each of these agents is small and inconclusive. The table below summaries the ***only*** published trials on MVP and vinorelbine and clearly shows that the robust results with pemetrexed are superior in terms of survival benefit and response rate.

Table 4. Reported Survival Outcomes and Tumour response for pem/cis and UK comparators in MPM

Study name	Interventions	Study design	No of patients	Tumour type	Overall median survival (months)	Response rate
[redacted]	Pem/cisplatin Vs cisplatin	Phase III trial Randomised single-blind, parallel arm	448	Malignant pleural mesothelioma	**ITT:** Pem/cis =12.1 Cis = 9.3 **FS:** Pem/cis = 13.3 Cis = 10.0	**ITT:** Pem/cis = 41% Cis = 17% **FS:** Pem/cis = 45% Cis = 19%
[redacted]	MVP	Non-comparative , prospective study	39	Malignant mesothelioma *(unclear whether pleural or peritoneal)*	6	PR: 20%
[redacted]	MVP	Non-comparative , prospective study	150	Pleural mesothelioma	7	15.3%
[redacted]	Vinorelbine	Phase II, non-comparative open-label study	29	Malignant pleural mesothelioma	10.6	PR: 24%
[redacted]	Vinorelbine and oxaliplatin	Phase II, non-comparative study	26	Malignant pleural mesothelioma	8.8	PR: 23%

ITT – intent-to-treat, FS – fully supplemented patients (pemetrexed licence mandates vitamin supplementation), PR – partial response, MVP – mitomycin+vinorelbine+platinum

(ii) Model 2 – inconclusive evidence base?

According to the ACD, the results of Lilly's Model 2 cannot be used to make a decision regarding the comparative cost-effectiveness of pemetrexed to MVP and vinorelbine because the evidence base for an economic analysis is, as described by the Assessment Group, 'not credible since it is not founded upon direct or even indirect comparisons of RCTs and there is no evidence to support the comparability of the patient populations between the various studies quoted nor with EMPHACIS'. The Assessment Group concluded there was no objective basis on which to estimate the survival gains of MVP and vinorelbine. However Model 2 does serve to highlight the lack of data available on MVP, vinorelbine and ASC in mesothelioma.

Model 2 was undertaken by Lilly at the specific request of NICE and LRiG. Model 2 was the first systematic attempt to review the evidence (clinical and UK market research data) on MVP, vinorelbine and ASC/best supportive care (BSC) in mesothelioma, pending the results of the MSO1 study. Therefore Lilly's request for Model 2 to be reviewed was for the purpose of providing a comprehensive assessment of the evidence base for MVP, vinorelbine and to show that any cost-effectiveness result would be highly sensitive to changes in the inputs. Lilly acknowledged that there was a high degree of uncertainty surrounding the results of Model 2 but made an honest pragmatic attempt to give an indication of the *potential/probable* range of ICERs for pemetrexed when compared to current 'best' practice.

The evidence base for Model 2 is the same evidence base supporting current 'best' practice as stated in the ACD. It appears inconsistent that the evidence base for MVP and vinorelbine are considered by NICE to be sufficient to support 'current best practice' in the UK, when a licensed proven alternative is available, and yet the very same evidence base is considered 'not credible' for use in an economic evaluation.

5. MSO-1 Clinical Trial and its applicability to the assessment of pemetrexed for mesothelioma and study JMFL

MSO1 trial was set up to show whether there was benefit of cytotoxic therapy over active symptom control (ASC) as there was doubt whether any chemotherapy was active in MPM.

A feasibility study which randomised 109 patients to one of three study arms ASC, ASC+MVP and ASC+ vinorelbine) was initially carried out between September 2000 and September 2001 (Muers, 2005). The oncolytics chosen were those for which there was some phase II evidence of benefit; at that time, two single-arm phase II trials existed, one in 29 patients (Vinorelbine) and one in 39 patients (MVP).

Based on the results of the feasibility study, the MSO1 trial itself commenced recruitment in July 2003 with a closure date of 31 May 2006 and a planned sample size of 840 patients, 280 patients per study arm (of which the data from the 109 patients from the feasibility study would be included). Due to issues of recruitment, a sample size of 420 patients is now proposed with the active treatment arms being combined vs ASC (see below). As at 14 February 2006, 93.6% of the target (NCRN website) had been recruited.

Pemetrexed was licensed in November 2004. At the time of designing the registration trials for pemetrexed, no cytotoxic chemotherapy had ever been licensed in mesothelioma. Consequently, Lilly consulted with its International panel of Clinical Advisors (including representation from the UK) and the US regulator, the Food and Drug Administration (FDA) to determine how the necessary trials should be designed. It was the considered opinion of both groups that on the evidence available at the time there **was** a role for chemotherapy in the management of mesothelioma and that the evidence for single-agent cisplatin was as strong as for any other chemotherapy regimen (Zidar 1988 & Mintzer 1988). Therefore a decision was made to have an active comparator arm rather than an ASC arm in the EMPHACIS trial. This consensus view was mirrored by the principal oncology research group in Europe – the EORTC – who very shortly afterwards developed a study in mesothelioma in which single-agent cisplatin was the reference arm. In a recent review of 83 clinical trials published from 1965 to 2001, cisplatin was found to be the most active agent and had the highest response rate (28.5%) in unresectable malignant mesothelioma (Berghmans et al 2002)

The results of the EMPHACIS trial were presented at ASCO in 2002 and caused considerable interest amongst clinicians. The MS01 investigators subsequently contacted Lilly to see if it was possible to include pemetrexed so that a fourth arm of pemetrexed/cisplatin could be included in the study.

Lilly considered this request in line with its Standard Operating Procedures (SOPs) on Investigator-Initiated Research. After extensive discussion at a corporate level it was considered, in line with our SOPs, that we were unable to participate in such a study as pemetrexed was not yet licensed for any indication in the UK and as it included an inactive arm (ASC).

In these circumstances the statement at paragraph 4.3.3 of the ACD that "pemetrexed was not included as a comparator in this study [MSO1] and heard that the manufacturer had not sanctioned its use" does not properly reflect the factual situation, and is unbalanced and unfair. Lilly therefore suggests that this paragraph of the ACD should end with the sentence "the committee observed that pemetrexed was not included as a comparator in this study". Should the Appraisal Committee wish to indicate that Lilly did not agree to the inclusion of pemetrexed in the MSO1 study it should properly explain why this is the case. The current draft of the ACD creates a false impression as to Lilly's reasons for refusal.

Whilst the results of MSO-1 will provide additional data on the use of chemotherapy and ASC in mesothelioma, we do not believe that it is relevant to the assessment of pemetrexed in malignant pleural mesothelioma, which has already been through regulatory processes and considered clinically effective.

JMFL study

In response to worldwide interest, following the ASCO presentation, Lilly developed a protocol for a corporate safety study, JMFL, which was designed to both meet the extensive demand for 'compassionate use' whilst also capturing important additional safety data and awaiting regulatory approval. It is important to note that Lilly did not actively recruit study sites. Only clinicians who made enquiries to Lilly for pemetrexed on compassionate use were provided with details of the study. Furthermore, they themselves had to ensure that the study received the approval of their hospital Ethics committee and Research & Development committees. Importantly, no payments were made for entering patients into the study, or for data collection.

The first patient in the UK entered JMFL in February 2003 and by November 2004 a total of 584 patients had entered the study from 34 sites. A large number of the sites were also involved in the MS01 study. We believe this rapid rate of enrolment reflects the level of UK clinicians' interest in this therapy.

Once pemetrexed was licensed for use in the UK, the JMFL study was closed; although, those patients still on study continued to receive free pemetrexed from Lilly for the remainder of their treatment.

6. Industrial disease and NHS Investment

Malignant pleural mesothelioma (MPM) is an occupational disease related to exposure to asbestos. The disease affected around 1,900 UK patients in 2001 and is expected to rise to around 2900 cases in 2010 and declining thereafter. This represents an unusual situation of a time-limited requirement for increased NHS expenditure for this condition.

On the basis that approximately half the patients with MPM receive chemotherapy: It is estimated that the introduction of pem/cis to treat MPM in the UK will cost £2.7 million in 2005/6, increasing to £5.2 million in 2009/10.

7. Summary

In conclusion, Lilly believes that the approach followed by the Appraisal Committee in considering pemetrexed is inconsistent with that followed in other similar appraisals and fails adequately to reflect the benefits of this product in the treatment of a disease for which no other therapy is authorised or has shown comparable effects.

(i) Lilly believes that all of the evidence available to the Appraisal Committee has not been appropriately taken into account.

In considering pemetrexed, the Appraisal Committee has assumed that all patients will continue on therapy for a full six cycles of the treatment, irrespective of response. This does not reflect clinical practice in England and Wales. The scope for this appraisal requires that the Appraisal Committee should consider stopping rules for treatment in the context of the clinical evidence base and any

economic evaluation. As demonstrated in this response, stopping treatment in patients who failed to respond to pemetrexed after four cycles of treatment would substantially reduce costs, without reducing the overall survive benefit of patients with MPM. Lilly believes that it is incumbent on the Committee adequately to consider these data before forming a final determination with respect to use of pemetrexed in NHS patients.

In addition to the clear survival benefits demonstrated in the RCT data for pemetrexed, the Appraisal Committee is also required to take into account the absence of any reliable data in relation to the comparators. Lilly believes that the approach of the Appraisal Committee in this context has been unbalanced and that informing a view that pemetrexed should not be recommended, the committee has failed to give adequate weight to the fact that there is no real evidence at all in support of use of the other therapies currently used to treat MPM patients in England and Wales.

Furthermore, MPM is a devastating disease, invariably associated with a fatal outcome and associated with particularly distressing symptomatologies. In view of the fact there is no other treatment currently licensed for this indication in the UK, the clinical need of such patients is very high indeed and this fact should be properly recognised by NICE consistent with the Secretary of State's directions, in formulating its guidance to the NHS.

Finally, the scope requires that evidence relating to patient choice in a non-curative setting should be considered. Submissions from patient groups and clinicians in this appraisal supported the inclusion of pemetrexed as a treatment option for MPM patients in England and Wales. The ACD does not explain how the substantial support for the product from patient groups has been considered by the Appraisal Committee in formulating its negative preliminary view.

(ii) Lilly does not believe that the summaries of clinical effectiveness and cost effectiveness are reasonable interpretations of the evidence.

Lilly believes that, for the reasons set out above, the summaries of the evidence contained in the ACD do not fairly reflect the benefit of pemetrexed therapy and the uncertainties associated with treatment with all other comparators.

Furthermore, the assessment of cost effectiveness is not fair or balanced in view of the inherent bias against incurable diseases and treatments used for patients with a short life expectancy, in forming a determination based on QALY values.

(iii) Lilly does not believe that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

It is evident from the above, that Lilly does not believe that the approach of the Appraisal Committee to date and the assessment of the evidence set out in the ACD form a fair or rational basis for the provision of guidance to the NHS. In particular, Lilly believes that it is inherently irrational that MPM patients in England and Wales should be deprived of the only medicinal product licensed in this country, with a statistically significant survival benefit demonstrated in RCT data in favour of alternative untested therapies to which there is no comparable evidence.

Should the institute or the Appraisal Committee have any additional queries in relation to Lilly's submissions or the use of pemetrexed, Lilly would be pleased to assist. We look forward to considering the FAD in due course.

Yours sincerely

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Head of HTA Strategy and Medical Advisor

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Appendix 1: Definition of Responders

Response	Disease Status	Criteria
Complete Response (CR)	Measurable and evaluable	Complete disappearance of all disease. No new lesions. No disease-related symptoms. No evidence of nonevaluable disease, including normalization of markers and other adnormal lab values.
Partial response (PR)	Bidimensionally Measurable Only	A decrease ≥50% under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease.
	Unidimensionally Measurable Disease Only	A decrease ≥30% under baseline in the sum of the greatest diameters of unidimensionally measurable lesions.
	Both Bi- and Unidimensionally Measurable Disease	A decrease ≥50% under baseline in the sum of products of perpendicular diameters of bidimensionally measurable disease (and no progression in the sum of the unidimensionally measurable lesions) or a ≥30% decrease under baseline in the sum of the greatest diameters of unidimensionally measurable lesions (and no progression in the sum of bidimensionally measurable lesions)