NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Pemetrexed disodium for malignant pleural mesothelioma

Response to consultee, commentator and public comments on the post appeal ACD

Consultee and Commentator response to the ACD

Consultee or commentator	Comments	Institute response
Eli Lilly and Co.	Our current concerns focus upon three key areas: equity for patients, the established benefit of chemotherapy in treating MPM and the balance of societal benefit over cost. *Equity* MPM is an occupational disease related to asbestos exposure, generally through employment in asbestos factories, shipbuilding (naval and civilian), railway carriage works, construction, coalmining and is therefore inherently associated with inequity due to higher rates of disease in manual workers and significant regional and national geographical variation in incidence across the UK, for example, the incidence in Scotland is a third higher than in England and Wales.[1,2] It is a disease associated with significant symptom burden and early mortality; life expectancy, if untreated, is between 5 and 8 months on average, and patients suffer from severe pain, induced by the tearing of the lungs from the chest wall, extreme weight loss and difficulty breathing. Death is usually caused by the person drowning from the fluid that collects in their lungs. Chemotherapy, in particular pem/cis, has been proven to extend life and improve quality of life for these patients. Pem/cis is the only licensed therapy for MPM. Lilly request that the appraisal committee place less emphasis on the need to demonstrate cost-effectiveness against a standard 'threshold' and instead take into consideration other important factors relating to equity, such as clinical effectiveness, unmet need, the severity of the disease, and innovation - all of which are useful measures of the value of a medicine.	The Committee considered these issues in appraising the technology see FAD 4.3.11. see FAD 4.3.11

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Eli Lilly and Co. (continued)	The industrial cause of the disease, the below average socioeconomic status of MPM patients, the severe nature of the disease and the innovation of pemetrexed therapy means that the provisional decision not to recommend pem/cis is not equitable for patients who rely upon the NHS for their terminal healthcare.	see FAD 4.3.11
	In addition, there is a subgroup of clinically recognisable patients with advanced disease, and good performance status in whom pem/cis would prolong survival by an average of 5 months (NICE assessment group estimate) and in whom cost-effectiveness was estimated at £37,664 by the external assessment group. This brings the cost-effectiveness of pem/cis within the ranges previously approved by NICE for cancer medicines. It is of note that the cost-effectiveness estimate based upon the use of the pemetrexed 100mg vial was £33,474. The pemetrexed 100mg vial will become available early next year.	see FAD 4.3.8
	The appraisal committee have understandably based their decision on what they believe is society's willingness to pay for an additional QALY. However, Lilly believe that the UK public would be willing to pay an additional £3000 -£7000 per QALY gained for an industrially caused terminal condition with 5-8 months life expectancy and poor quality of life.	The Committee considered this issue in appraising the technology, see FAD 4.3.11
	Lilly would like to highlight that the use of pem/cis for MPM has already been recommended by several bodies in the UK –The Cochrane Collaboration, London Cancer New Drugs Group, the Drugs and Therapeutics Bulletin, and the Scottish Medicines Consortium (SMC).	The Committee was aware of the recommendations of other bodies (not all of whom consider clinical and cost-effectiveness).

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Eli Lilly and Co. (continued)	*Established benefit of chemotherapy* Evidence suggests that chemotherapy provides significant survival benefits over and above Best Supportive Care/Active Symptom Control (BSC) in the treatment of MPM (O'Brien[3] *et al*, 2006). Pem/cis has a proven survival benefit over cisplatin, an active agent, in a phase III randomised controlled trial (RCT), endorsed by regulatory authorities all over the world. Cisplatin was the comparator arm in the trial because it was not deemed ethical by regulators to compare to BSC on the basis that cisplatin is an active thoracic oncolytic agent and therefore at least equal to BSC in terms of efficacy. Pem/cisplatin has been proven to provide greater survival benefits than cisplatin alone. Therefore survival benefit with pem/cis can be assumed to be greater than BSC.	Noted – see FAD 4.3.6
	It is not now ethical or feasible to conduct a trial versus BSC in this indication. All future clinical trials will now have to compare new medicines to pemetrexed as the standard of care (e.g. pem/cis monotherapy compared to pem/cis in combination with new agent). Lilly are therefore, surprised at the statement in the ACD that this question still has to be resolved via RCTs. Lilly suggest that an independent clinical audit aimed at collecting data on the clinical effectiveness of pem/cis in MPM in a 'real world' context would be more appropriate and pragmatic than a RCT.	Noted – however further evidence relating to the comparison of pemetrexed with other effective or potentially effective regimens is required
	Balance of societal benefit over cost The number of newly diagnosed cases of mesothelioma per year in the UK is approximately 2500, of which 80% are of MPM; only half of these MPM patients would be eligible to receive chemotherapy. It is estimated that the introduction of pem/cis to treat MPM in the UK would cost a maximum of £4.2 million in 2007-2008 increasing to £5.2 million in 2009-2010. This is a low budget impact. Significantly, MPM represents an unusual situation of a time-limited requirement of increased NHS expenditure for this condition. Various other unlicensed chemotherapy regimens lacking robust evidence of clinical benefit are also still being prescribed under the NHS. The current draft recommendation could result in the continued funding of these unproven treatments which ignores the regulatory licensing process and constitutes a poor use of NHS resource.	The Committee bases its decisions on clinical and cost effectiveness

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Eli Lilly and Co. (continued)	It is of concern to Lilly, asbestos victim support groups and society in general that for a medicine licensed in November 2004, if current provisional advice were to hold, the vast majority of patients may not have access to a life-extending innovative medicine until 2009 at the earliest, five years after the medicine was first licensed. I note the re-review date for this therapy is March 2008. Lilly welcome this early re-appraisal. However, in order to obtain robust data to add to the evidence base on pemetrexed in MPM in the UK, sufficient time is needed to collect such data. In alignment with the recently published Department of Health's *Mesothelioma Framework*, real world effectiveness data on pem/cis could be collected in a clinical audit setting within the NHS. We would be happy to have a discussion with NICE on the possible date for re-review on the basis of new data that may be available.	Noted
	Lilly hope that the appraisal committee will re-evaluate its decision not to recommend pemetrexed/cisplatin for the treatment of MPM and will understand the benefit this will offer to MPM patients and society as a whole. Our comments regarding the appraisal committee's interpretation of the available evidence are outlined in paragraphs below.	Noted
	1. The appraisal committee's decision is inequitable for pem/cis in the subgroup of fully supplemented, good performance status and advanced disease patients 1.1 Identification of patients with advanced disease is feasible in clinical practice As per paragraph 4.3.7 of the ACD, clinical experts stated that 'most people with MPM present with advanced disease judged on the basis of pragmatic staging criteria using non-invasive imaging techniques'. Therefore Lilly believe that differential staging of the disease is not a requirement for identifying the subgroup of patients with advanced disease for pemetrexed treatment and the subgroup of advanced and therefore inoperable disease can be clearly identified in clinical practice. This subgroup was specifically analysed to represent the UK patient population, on that basis that MPM patients are treated in specialised centres with sufficient expertise in identifying advanced patients. The opinion of the clinical experts attending the appraisal committee validated this and it is of concern that insufficient weight has been given to the evidence from clinical experts.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.

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Eli Lilly and Co. (continued)	1.2 Rejection of cost-effectiveness based on post-hoc analysis The appraisal committee also dismiss the results of cost-effectiveness in the fully supplemented subgroup of patients with good performance status and advanced disease, as being unreliable having been based on a post-hoc analysis of trial data. This sub-group consists of a robust sample of 207 patients from the registration trial. Lilly were encouraged by NICE at the consultees meeting held prior to the appraisal to identify the subgroups of patients in whom the intervention would have the greatest cost-effectiveness. Indeed, the Liverpool external review group (LRiG) specifically requested sub-group analyses in their protocol for the assessment of pemetrexed "Clinical effects in subgroups of patients will be explored". It is with interest that Lilly note this subgroup analysis was not rejected by the Assessment Group in its review of pemetrexed, nor did the appraisal committee raise this concern in the first ACD and FAD for pemetrexed. Lilly request an explanation of this discrepancy in the appraisal in view of the fact that NICE has previously accepted post-hoc analyses as a basis for positively recommending other technologies. In view of the above-mentioned arguments, Lilly request the appraisal committee to reconsider the use of pem/cisplatin in the subgroup of fully supplemented patients with good performance status and advanced disease. *2. Consideration of cost per QALY in preference to cost per life year gained (LYG)* 2.1 Lung cancer utility estimates used in the economic model did not capture the differences between symptom relief and improvement in quality of life with pem/cis and cisplatin alone in MPM patients: In the absence of utility estimates for MPM, the economic model submitted by Lilly used advanced lung cancer utility estimates adjusted for performance status. Thus, the benefits of symptom relief and the improvements in quality of life for pem/cis patients were not included in the QALY estimate, which means that the QALY gain estimated for pem/cis was conservative and underestimated the real QALY gain for these patients. Lilly believe that the use of a cost-effectiveness analysis using cost per LYG estimates in preference to a cost-utility analysis is particularly relevant in this case since no utility estimates exist for MPM. Whilst we agree with the appraisal committee's conclusion that the utility estimates used in the model are a 'fair approximation' of the utility values for people with MPM we do not agree that these fairly represent the differences between the two therapies in terms of tumour response and symptom burden.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate. see FAD

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Eli Lilly and Co. (continued)	The decision of the appraisal committee to use cost per QALY was also based on the assumption that any uncertainty surrounding the surrogate utility values had been adequately assessed by the Assessment Group. However, this assumption may be flawed since the PSA undertaken by the Assessment Group was what they describe as an 'indicative PSA'. One of the parameters assessed was utility using a normal distribution when in fact a log normal would have been more appropriate. Further, the Assessment Group were unable to assess the covariance between parameters, in particular survival and drug cost (page 75/76 of the evaluation report).Given the limitations around the cost per QALY estimates used in this appraisal, Lilly request that the appraisal committee reconsider their decision not to use cost per LYG in this particular case. *3. Pemetrexed compared to best supportive care / other chemotherapy regimens* Lilly agree with the appraisal committee's assertion that, in principle, additional clinical research comparing pem/cis to other chemotherapy regimens is desirable, particularly in a 'real-world' setting. However, from a pragmatic standpoint, we would like to emphasise that in terms of additional clinical trial evidence: i) pem/cis has become the standard of care for MPM patients across the developed world, and is a valid comparator for drugs under development for MPM. Ethics dictate that a trial of pem/cis vs. BSC at this stage would not be permissible. ii) the clinical benefits of pem/cis in MPM have been already established by the trial vs. cisplatin alone. Therefore it follows that pem/cis offers survival benefits over BSC and an additional trial comparing pem/cis vs. BSC is neither required nor as mentioned above, ethical. (iii) The cost and benefits of requiring further clinical trials in order to add to the evidence base has not been quantified by NICE (i.e. expected value of perfect information / cost of reducing uncertainty in CE estimates). This is particularly relevant in terms of the low budget impact associated with this medicine. The value of information gained from any trials comparing pem/cis with other chemotherapy regimens used in the treatment of MPM is questionable since the efficacy of pem/cis in this setting has already been established.	see FAD 4.3.7 and 4.3.11 See FAD 4.3.6

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Eli Lilly and Co. (continued)	(iv) From the above, it is clear that no additional clinical trial data is expected before the scheduled re-review of pem/cis for March 2008. However, given the devastating nature of MPM it is clearly in the interest of patients to provide answers to clinical questions that the appraisal committee feel, remain unanswered. Lilly are of the opinion that additional data on pemetrexed may be collected by recommending the use of pemetrexed and collecting the additional data through a clinical audit within the NHS. This would be aligned with the current Department of Health *Mesothelioma Framework* and would enable continued research into the benefits of pemetrexed in a real world context. The clinical data from such research would provide additional evidence for NICE to re-assess.	Noted – given the change to the guidance the Committee did not feel it necessary to change the review date.
British Mesothelioma Interest Group (consultee) and British Thoracic Oncology Group (commentator)	We are very disappointed with the ACD that rules that pemetrexed disodium is not recommended for the treatment of malignant pleural mesothelioma. From a clinical standpoint, the recruitment of approximately 450 patients with a rare tumour into an International Phase III Clinical Trial over such a short period of time is to be applauded. The trial demonstrated a statistically significant benefit for the use of pemetrexed in combination with cisplatin, compared with cisplatin alone. Pemetrexed is now the only licensed treatment for mesothelioma, a fatal malignancy inevitably caused by asbestos exposure. The use of cisplatin as a control arm has been criticised. Whilst this is not a commonly used single agent for the treatment of mesothelioma in the England and Wales, it is commonly combined with other agents at the current time for patients with this disease, most notably mitomycin and vinblastine (MVP). Indeed, a meta-analysis (Berghmans, 2002) suggested that cisplatin was the most active drug for mesothelioma so this is not an inappropriate control treatment for the Phase III trial.	See FAD 4.3.3

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British Mesothelioma Interest Group and British Thoracic Oncology Group (continued)	There are no randomised trials that have been published that compare chemotherapy with active symptom control – this is being investigated in the MSO-1 trial. However, the chemotherapy regimens used in this trial (either MVP or vinorelbine) were based on very small Phase II clinical trials. Therefore, the result of this trial is not going to help shed light on whether chemotherapy is superior to active symptom control. The incidence of mesothelioma in the UK is likely to increase over the next 5-10 years, after which it is likely to decline significantly. It is imperative that this is considered – this is not a malignancy that is likely to have a huge impact on the resources of the NHS for years to come. Much is said about recruitment into clinical trials and, as Oncologists, we are continually encouraged (rightly) to enrol patients into appropriate clinical trials. Despite many centres around the World recruiting into the Phase III trial, it is hugely frustrating that the result, a significant one, is going to have no effect on the clinical practice of a hugely distressing disease. The Appraisal Document identifies a need for randomised controlled trials comparing alternative treatment regimens in MPM – this has been done (see above) and the results will have no impact on clinical practice. The Committee recommends that trials be conducted in which pemetrexed is compared with treatments currently commonly used in England and Wales (notably MVP, vinorelbine and active symptom control) in order to determine its relative effectiveness. Pemetrexed has been tested in combination with cisplatin versus cisplatin alone (the likely most active drug of the MVP combination). It is difficult to justify a clinical trial that would use the only licensed drug in mesothelioma and compare this with active symptom control – recruitment would be near impossible. The time taken to conduct these trials would mean this is a huge backward step for the treatment of this disease. The Committee also suggests that comparative trials of pemetrexed versus other promising agents be conducted – whilst this is a reasonable suggestion it is hard to see how this will be possible if pemetrexed is not allowed to be routinely prescribed.	Noted

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British Mesothelioma Interest Group and British Thoracic Oncology Group (continued)	In addition, we feel the cost effectiveness data are incredibly complex and we are not sure exactly how reliable these are. In summary, we feel the guidance is hugely disappointing for mesothelioma sufferers and the Oncologists and other members of the healthcare profession who work so tirelessly to improve the lives of this unfortunate group of patients.	
British Thoracic Society	I thank you for this opportunity to comment on the 2007 document: Health technology Appraisal: Pemetrexed disodium for the treatment of mesothelioma: Appraisal Consultation document. This is the 2007 appraisal document and I note that the appraisal committee's conclusions are the same as those reached after the first appraisal. The appraisal has been repeated after some appeals to NICE. I note that from the technical standpoint, the major question to be answered was whether the appraisal committee concluded after review that QALYs were an appropriate measure to use when coming to conclusions about cost-effectiveness of chemotherapy in malignant mesothelioma (MPM). The appraisal committee has concluded that in its opinion they are. I note that on the present evidence as I understand it, on the grounds of the limited cost-effectiveness, the appraisal committee may not in its final decision, approve Pemetrexed plus Cisplatin as treatment for MPM in England and Wales at the present time. If this is the final conclusion, I would suggest that, for the benefit of future patients: 1. The appraisal committee have stated that they wish to re-visit this appraisal and give us a suggested starting date of March 2008. May I suggest that an appropriate date in fact might be when the 400-patient randomised controlled trial MSO1 supported by the British Thoracic Society and the MRC, and now closed to recruitment, has been fully published, to include the quality of life data therein obtained. It is my opinion that it is unlikely that the publication in a peer review journal will occur before March 2008 and it is almost certainly to be a little later than this. I would suggest the committee might set a later date for review, perhaps the summer of 2008 or thereabouts.	Noted – given the change to the guidance the Committee did not feel it necessary to change the review date.

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	2. Patients should be assured by NICE that other chemotherapy for MPM, already widely used in the United Kingdom, such as for example Vinorelbine as a single agent or Gemcitabine and Cisplatin, and cheaper than Pemetrexed, do show the occasional marked and definite and helpful individual response. There is no reason why a patient wishing to have chemotherapy should not have first or even second line treatment with one or more of these regimens. 3. The BTS would welcome more emphatic support (as in section 4.3.11) for the contention that in view of the uncertainty surrounding the cost-effectiveness of Pemetrexed plus Cisplatin, there is a strong case for funding bodies to support a large clinical trial in the UK of this combination vs a comparator or comparators, depending upon the forthcoming results from the MSO1 study.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.
Department of Health	In our view, we feel that the Appraisal Committee's summary recommendation (1.1) that: *"Pemetrexed disodium is not recommended for the treatment of malignant pleural mesothelioma"* is in contrast to the 'plain language summary' of the 2007 Cochrane review of the same drug in the same condition1, which stated *"Pemetrexed disodium…….significantly increases the length of survival, as well as relieves symptoms of mesothelioma."* Paragraph 2.7 of the ACD states that there is no published evidence showing a survival benefit of chemotherapy over and above Active Supportive Care. We are of the view that, whilst it is true that no such randomised trial is yet published (the MESO-1 trial results are due to be presented at ASCO in May 2007), Pemetrexed demonstrated a survival benefit when compared with single agent cisplatin; an agent with marginal trial evidence to support its efficacy, which for practical purposes could justifiably be equated with Active Supportive Care. The results of the MESO-1 trial could influence the Committee's view on this issue. It would be helpful if the Committee could consider delaying the issue of any further guidance, until this has been taken into account.	The guidance will be considered for review in March 2008. The availability of these data will be considered at this time.

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	When applying the utility scores as part of the cost-benefit analysis, would you please consider taking into account improvements in quality of life. In our opinion, such improvements have been demonstrated to be associated with Pemetrexed treatment in the EMPHACIS trial. We understand that the Technology Appraisal Group used six cycles of Pemetrexed in their cost calculations. In our opinion, it would be unusual for a UK oncologist to continue treatment beyond four cycles, if there was no response or progressive disease. Therefore, the mean number of cycles likely to be prescribed in clinical practice will be less than six, resulting in a proportionally lower cost estimate. Although we do appreciate that there will be certain circumstances when, for reasons wider than simple cost, it might be appropriate to recommend a particular technology. However, we feel that there are several reasons why the Committee should consider taking other factors into consideration in the case of Pemetrexed. These include: a) This is a relatively small patient group; therefore the cost impact on the NHS will be small. It is highly unlikely that there will ever be more than 1500 new cases of malignant pleural mesothelioma in England per annum. Informal surveys and preliminary audit data suggest that no more than 30% of these patients receive chemotherapy currently in the UK. Therefore, the total cost to the NHS in England (depending on the number of courses used per patient) would be perhaps £2m - £3m per annum. b) This is a patient group, who have contracted their fatal disease as a consequence of their occupation. c) Mesothelioma is a disease for which there is currently virtually no good evidence-based treatment. Reference: 1. (http://www.thecochranelibrary.com: (2007) 'Pemetrexed Disodium in combination with cisplatin versus other cytotoxic agents or supportive care fro the treatment of malignant pleural mesothelioma (Review)'.	See FAD 4.3.11 See FAD 4.3.11

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Mesothelioma UK	*1.0 Introduction* Mesothelioma UK represents the views of patients with mesothelioma and their carers plus those of a number of specialist clinicians from a wide variety of disciplines who care for such patients. We are dismayed and perplexed by the decision of the Appraisal Committee as stated in their ACD released in March 2007.	
	2.0 Unlicensed drugs and the clinicians' dilemma Pemetrexed is the only licensed agent for the treatment of malignant mesothelioma in the UK. If the NHS were forced to follow this NICE guidance, clinicians would have two options: a) not to offer chemotherapy of any sort to such patients, or b) to prescribe unlicensed drugs or drug combinations for which there is less evidence of benefit than that available for Pemetrexed. Given the fact that it is undisputed that a proportion of patients with mesothelioma do benefit, albeit to a modest extent, from chemotherapy, NICE is, for practical purposes, promoting the use of unlicensed products.	Noted
	3.0 Conflict with the Cochrane Review[1] The Appraisal Committee's summary recommendation (1.1) that: "Pemetrexed disodium is not recommended for the treatment of malignant pleural mesothelioma" is in stark contrast to the 'plain language summary' of the 2007 Cochrane review of the same drug in the same condition[1] which stated; "Pemetrexed disodium…significantly increases the length of survival, as well as relieves symptoms of mesothelioma." The first author of this Cochrane review was one Dr J Green – the only clinical member of the Liverpool Technical Appraisal Group. We assume that this means he does not agree with the findings of the appraisal group of which he is a member.	The Appraisal considers cost-effectiveness as well as clinical effectiveness. The Cochrane review is a systematic review of the clinical evidence.
	4.0 Studies vs. ASC and the MESO-1 trial Paragraph 2.7 states that there is no published evidence showing a survival benefit of chemotherapy over and above Active Supportive Care. Whilst it is clearly true that no such randomised trial is yet published (the MESO-1 trial results are due to be presented at ASCO in May 2007), Pemetrexed clearly demonstrated a survival benefit when compared with single agent cisplatin; an agent with marginal trial evidence to support its efficacy, which for practical purposes could justifiably be equated with Active Supportive Care. We believe the results of the MESO-1 trial could influence the Committee's view on this issue and we would urge them to delay issuing further guidance until this has been taken into account.	The Committee considered this issue in appraising the technology, see FAD 4.3.6

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	5.0 Quality of Life benefit We are puzzled why the Committee has taken no account of the improvements in Quality of life that have been clearly demonstrated to be associated with Pemetrexed treatment in the EMPHACIS trial, particularly when mesothelioma is such a symptomatic disease. Why is this 'Quality' measure not taken into account when applying the (highly speculative) utility scores as part of the cost-benefit analysis?	See FAD 4.3.11
	6.0 NICE cost per QALY threshold in patient groups with a very poor prognosis We believe that the current method of assessing the cost per QALY which only looks at the absolute gain in survival time, rather than that improvement relative to the median overall survival of the population, results in cost estimates which will almost invariably exceed the £30,000 barrier in patients whose median survival is measured in months. Surely a 3-month survival gain in a population with an untreated expected survival of less than 9 months is relatively more valuable (to patients and carers) than an improvement of a similar magnitude if it occurred in a disease with a 5 year median survival? Because this *relative survival* improvement is never used, new therapies in mesothelioma and advanced Non Small Cell Carcinoma are almost always doomed to fail the 'NICE' QALY test. Indeed it is likely that all previous advances in treatment in these two diseases would have been rejected by NICE had such analyses been applied in the past. If this fundamental flaw in the analyses is not addressed it will have a major stifling effect on research at all levels because it will be clear to everyone that the results of any research of this sort in patients with advanced disease is highly unlikely to be translated into clinical practice. It might also be considered to make such research unethical since it could never change practice.	See FAD 4.3.11
	7.0 Number of cycles The Technology Appraisal Group has insisted on using 6 cycles of Pemetrexed in their cost calculations. It is our view, having talked to many oncologists in the field, that it would be highly unusual for a UK oncologist to continue treatment beyond 4 cycles if there was no response or progressive disease. Thus the mean number of cycles likely to be prescribed in clinical practice will be less than six, resulting in a proportionally lower cost estimate.	See FAD 4.3.5

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	8.0 Wider benefits and cost impact NICE recognises that there will be certain circumstances when, for reasons wider than simple cost, it might be appropriate for them to recommend a particular technology. We believe there are several reasons why the Committee should consider taking other factors into consideration. These include: a) This is a relatively small patient group and thus the cost impact on the NHS will be small. It is highly unlikely that there will ever be more than 1500 new cases of malignant pleural mesothelioma in England per annum. Informal surveys and preliminary audit data suggest that no more than 50% of these patients receive chemotherapy currently in the UK, thus the total cost to the NHS in England (depending on the number of courses used per patient) would be perhaps £3m - £4m per annum. (Currently Herceptin in Breast Cancer is costing the NHS between £9-10m per *month*) b) Mesothelioma is treated in the UK by specialist oncologists who are not noted for taking an irresponsible or extreme position in their use of news drugs. They are, via the NCRI, actively involved in clinical trials and we are confident that they would use Pemetrexed in a responsible fashion only in those patients whom they felt would be most likely to benefit. To add to this, the Department of Health has recently published its National Mesothelioma Framework which addresses the issue of optimum service delivery for the management of this disease. One of its most important recommendations is the establishment of a small number of Specialist Mesothelioma MDTs – approximately one in each of the 32 English Cancer Networks. This would lead to an even more specialist level of management and probably result in even more cautious use of this new agent. These factors should help limit the cost impact of a recommendation to allow the use of Pemetrexed in Mesothelioma.	The Committee considered these issues in appraising the technology

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	c) This is a patient group who have contracted their fatal disease as a result of their occupation and through no fault of their own. A large proportion of them were exposed to the asbestos during the course of working in Government employment – especially in the armed forces. The UK Government was very slow to bring in asbestos control regulations: the 'Control of Asbestos at Work' legislation only came into force in 1981 and imports of Asbestos were not banned until 1999. Thus the Government has to take significant responsibility for this disease and allowing patients to receive the only chemotherapy for which there is randomised controlled trial evidence of benefit would seem to be the least that they can do as recompense. d) As stated in a number of different ways above, mesothelioma is a disease for which there is currently virtually no good evidence-based treatment. Now that we do have such a treatment (that is endorsed by a recent systematic Cochrane Review) it seems perverse in the extreme to deny this small group of patients a treatment that has significant potential benefits for them. Denying it to the NHS places clinicians in an almost impossible position – particularly when it is available in Scotland and virtually all other countries in the Western world. Reference: 1. (http://www.thecochranelibrary.com : (2007) 'Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care fro the treatment of malignant pleural mesothelioma (Review)'.	See FAD 4.3.11 The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.
National Lung Cancer Forum	The National Lung Cancer Forum for Nurses are extremely disappointed in the decision that has been made by NICE with regard of Pemetrexed disodium for the treatment of malignant pleural mesothelioma (MPM), to patients with an incurable, industrially caused, and painful disease. The views of patient representatives and clinicians do not seem to have been taken into account. The 'patient choice' agenda has been ignored as this decision gives patients no choice. The 'postcode lottery' has been enforced by this decision as this drug is available to patients in Scotland and is the standard of care in most of the developed world.	

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	Life expectancy, if untreated, is on average, between 5 and 8 months, and patients are likely to suffer from many disturbing symptoms including severe pain, extreme weight loss and extreme breathlessness. The committee discussed and compared the financial and survival benefits of other treatments that are commonly used in this disease but have not taken into account quality of life benefits or comparisons. The National Lung Cancer Forum for Nurses urges the appraisal committee to re-evaluate its decision not to recommend pemetrexed disodium for the treatment of patients with mesothelioma. This group of patients are victims of our industrial heritage and shouldn't be left to feel their suffering is unworthy of treatment that is available elsewhere in Europe.	See FAD 4.3.11
Royal College of Nursing	Thank you for the opportunity to review the Appraisal Consultation Document on the use of Pemetrexed Disodium for the treatment of mesothelioma. We are disappointed that the preliminary recommendations of the Appraisal Committee have again failed to address the needs of patients with this condition. The following comments are submitted with respect to the specified sections of the Document: Section 4.1.4 - NICE states that pemetrexed and cisplatin improved survival by 3 months – this represents a maximum survival benefit of 50% if, one accepts the literature that quotes an average survival of 6 months or a minimum of 25% improvement in respect of the literature that quotes an average survival of 12 months. Section 2.7 - The first statement is inaccurate. The standard chemotherapy treatment for MPM in Scotland is pemetrexed and cisplatin.	4.1.4 reports data from the study The Committee was aware of the outcome of the SMC evaluation

Consultee or commentator	Comments	Institute response
	The recommendations appear to have ignored clinical specialists' opinion on the use of this health technology. Does this mean that UK's leading lung oncology experts were all wrong? Does the Appraisal Committee understand how 'low the bar is with Mesothelioma'? Patients are looking for small improvements in treatment options to improve their quality of life and hopefully length of life. They enter into treatment fully informed. The Department of Health's current policies promote patient choice. The Appraisal Consultation Document appears to have ignored this. The number of Mesothelioma patients who are likely to require access to Pemetrexed is small and therefore the overall cost will not be unmanageable and would not set to increase drastically. Oncologists are cost conscious and most would not use such agent in futile situations. Pemetrexed is the only licensed agent for the treatment of malignant mesothelioma in the UK. Given the fact that it is undisputed that a proportion of patients with mesothelioma do benefit from the use of this health technology; albeit to a modest extent, if the NHS were forced to follow this proposed NICE guidance, in our view, NICE is for practical purposes, promoting the use of unlicensed products. Further, we believe that the 'postcode lottery' has been enforced by this decision as this drug is available to patients in Scotland, even though that the appraisal has been undertaken by two different bodies. The patients are still from one country – UK and should be treated the same. As stated in a number of different ways above, mesothelioma is a disease for which there is currently virtually no good evidence-based treatment. Now that we do have such a treatment (that is endorsed by a recent systematic Cochrane Review as well as reviews and endorsements by the Scottish Medicine Consortium and the London New Cancer Drugs Group) it seems perverse in the extreme to deny this small group of patients a treatment that has significant potential benefits for them. Denying it to the NHS places clinicians in an almost impossible position – particularly when it is available in Scotland and virtually all other countries in the Western world. We would urge the Committee to reconsider these recommendations.	See NICE Social Value Judgements guidance Principle 11 (available from URL http://www.nice.org.uk/page.aspx?o=283494) The Committee was aware of the outcome of the SMC evaluation

Consultee or commentator	Comments	Institute response
Tenovus Oncology Nurse Specialist Lung Cancer.	Thank-you for Forwarding the evaluation report. Tenovus welcomes the opportunity to comment and contribute to this process. An early review date should be set once the results of the MS01 trial are reported. From my experience of 13 years of working with patients with Mesothelioma, caution should be taken when offering chemotherapy to these patients unless they are functioning at a high level of performance status. The majority of patients are already experiencing all of the difficult symptoms associated with MPM at the time of diagnosis. Offering chemotherapy can result in unachievable high expectations in survival outcomes and a reduction in their quality of life. Patients and their families need to be informed of the benefit and toxicity impacting on their quality of life.	Noted – given the change to the guidance the Committee did not feel it necessary to change the review date.
Cancerbackup	CancerBACKUP welcomes the opportunity to contribute to the appraisal of pemetrexed disodium for the treatment of malignant pleural mesothelioma. As the leading specialist provider of independent information on all types of cancer, CancerBACKUP has regular contact with people living with mesothelioma and those caring for them. CancerBACKUP received 389 enquiries between 2003 and 2004 about mesothelioma and its treatment. CancerBACKUP believes that everyone with cancer should be offered the most effective and appropriate treatment, based on the available evidence and the patient's own wishes and preferences. We believe that: • Patients should have access to the most effective treatments appropriate to them as individuals; • Patients should be able to choose – in partnership with their oncologist – the treatment that is likely to suit them best in terms of relative benefits and side-effects; • The impact of treatments on patient's quality of life, as well as length of life, should be given full consideration by the Appraisal Committee. We urge the Appraisal Committee to recommend that pemetrexed disodium should be made available for patients for the treatment of malignant pleural mesothelioma.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.

Consultee or commentator	Comments	Institute response
Cancerbackup (continued)	*Living with mesothelioma* An estimated 1,700 people in the UK are diagnosed with mesothelioma each year. Mesothelioma is a cancer of the mesothelium. The mesothelium is a thin membrane that lines the chest and abdomen and surrounds the organs in these areas. The lining around the lungs is called the pleura and in the abdomen it is known as the peritoneum. Mesothelioma of the lining of the lungs (pleural mesothelioma) is much more common than mesothelioma in the peritoneum and for every person with peritoneal mesothelioma there will be about 12 people who have pleural mesothelioma. *Pleural mesothelioma* The pleura has two layers: the inner (visceral) layer, which is next to the lung and the outer (parietal) layer, which lines the chest wall. The two layers of the pleura are usually in contact and slide over each other as we breathe. The membranes produce fluid, which allows them to slide over each other easily. When a mesothelioma develops in the pleura (pleural mesothelioma), the delicate membranes thicken and may press inwards on the lung. Fluid may also collect between the two layers of the pleura and this is known as pleural effusion. *Causes* Up to 9 out of 10 cases of mesothelioma are caused by exposure to asbestos. When asbestos is disturbed or damaged, it releases tiny fibres that can be breathed into the lungs and cause inflammation, a build up of scar tissue and sometimes cancer. Mesothelioma does not usually develop until 10-60 years after exposure to asbestos and for this reason it is often difficult to discover the exact cause. As mesothelioma develops so slowly it is estimated that by 2020 approximately 3,000 people will be diagnosed with mesothelioma each year. The number of people who develop the disease will then start to reduce each year.	

Consultee or commentator	Comments	Institute response
Cancerbackup (continued)	*Symptoms* Mesothelioma often starts as many tiny lumps (nodules) in the pleura, which may not show up on scans or x-rays until they are quite large. The main symptoms of pleural mesothelioma are pain in the chest and breathlessness. Some people also notice their voice becomes hoarse and they have a cough that does not go away. Pleural mesothelioma can cause other general symptoms such as loss of appetite, weight loss and tiredness. *Staging of mesothelioma* There are several staging systems for pleural mesothelioma. An outline of a commonly used system is described below: Localised malignant mesothelioma. Stage 1 – The cancer cells are found in the pleura near the lung and heart or in the diaphragm or the lung Advanced malignant mesothelioma Stage 2 – The cancer has spread beyond the pleura to lymph nodes in the chest Stage 3 – The cancer has spread into the chest wall, the centre of the chest, the heart, through the diaphragm or abdominal lining and in some cases into nearby lymph nodes Stage 4 – The cancer has spread to distant organs or tissues *Treatment* Surgical resection is possible in a minority of patients but fewer than 15 percent of these patients live beyond five years. For those who are not treated with curative resection, the median survival duration when receiving best supportive care alone has been reported as six months, whereas the median survival time of 337 patients in 11 multicentre chemotherapy trials was seven months. Treatment with radiation therapy has been equally disappointing, in part because of difficulties in irradiating disease while avoiding toxicity to normal lung, cardiac and spinal cord tissues.	

Consultee or commentator	Comments	Institute response
Cancerbackup (continued)	*Pemetrexed disodium* Pemetrexed is a multitargeted antifolate and works by slowing the growth of tumours. CancerBACKUP argues strongly that NICE should recommend that pemetrexed disodium in combination with cisplatin are available on the NHS for the treatment of patients with mesothelioma in accordance with their licences as it can extend survival. A phase III study in malignant pleural mesothelioma compared treatment with cisplatin and pemetrexed with cisplatin alone. Median survival time was at 12.1 months for the combination arm compared to 9.3 months for cisplatin alone. This was a statistically significant difference. As with survival duration, the median time to progressive disease was significantly longer for patients who received pemetrexed and cisplatin as compared with patients who received cisplatin alone (5.7months compared to 3.9 months). The median time to treatment failure was also significantly longer in the pemetrexed/ cisplatin arm than in the control arm. *Adverse effects experienced with pemetrexed* Although pemetrexed can improve survival, trial data suggests that patients receiving pemetrexed in combination with cisplatin can experience severe toxicity. In patients receiving cisplatin as a single agent, severe toxicity was uncommon. In the pemetrexed/cisplatin arm grade 3/4 neutropenia and grade 3/4 leukopenia were the most common haematologic toxicities. However, patients who received vitamin supplementation had a notable reduction in haematologic toxicity, specifically grade 3/4 neutropenia and leukopenia. Overall improvement in severe toxicity has been observed in other pemetrexed studies because vitamin supplementation has become a standard of pemetrexed therapy.	See FAD 4.1.4 Refer to summary of product characteristics for details of side effects
NHS Quality Improvement Scotland	Section 1.2 makes an unprecedented statement to allow patients who are receiving treatment to continue. I would ask NICE to explain why they have made that statement.	The Institute considers that NHS patients who have already started treatment in good faith should not have their treatment withdrawn as a result of the conclusions of the Appraisal Committee or the Institute.

Consultee or commentator	Comments	Institute response
NHS Quality Improvement Scotland (continued)	In Section 2.5. The statement "There is no standard treatment pathway for MPM in the UK" is not accurate. In Scotland patients are offered chemotherapy with pemetrexed and cisplatin for advanced disease if they have good performance status, confluent with SMC Guidance.	The Committee was aware of the outcome of the SMC evaluation
	Section 2.7. The first statement is inaccurate. The standard chemotherapy treatment for MPM in Scotland is pemetrexed and cisplatin.	Comment noted
	Section 2.7 In the last statement the ACD states that there are no published randomised trials comparing this is not true. The reference is O'Brien MER et al. A randomised trial in malignant mesothelioma or early versus delayed chemotherapy in symptomatically stable patients. The MED trial. Annals of Oncology, 2006, 17: 270-275. The large national randomised trial of chemotherapy versus BSC is going to be reported in June at the ASCO meeting.	
	Section 3.4. They cannot assume 5 treatment cycles. In Scotland most clinicians would administer only 4 which would reduce the QALY. The ACD states that they could not substantiate the clinical experts' opinion that this was the case. On one hand the ACD takes the word of the clinical experts that there is no standard treatment pathway but refute the same clinical experts who say no-one gets 5 cycles.	See FAD 4.3.9. The mean number of cycles in the randomised trial was 6.
	Section 4.1.4. NICE state that pemetrexed and cisplatin improved survival by 3 months with improvements in QOL in the key trial. I would remind them that taxol (and carboplatin) was approved for advanced non small cell lung cancer with less of an improvement in survival. As such the appraisal is too influenced by cost alone. There is a strategy for the company to discount in advance of the launch of a smaller vial which will reduce the QALY.	The introduction of a smaller vial will influence cost but not the QALY gain.
	Section 4.2.5. The assumption the ASC/BSC costs would be the same in chemotherapy treated patients as non-chemotherapy treated patients is wrong. They state themselves in 4.1.6 that QOL improved in pemetrexed and cisplatin treated patients, thus the uptake of ASC/BSC by those patients will fall.	

Consultee or commentator	Comments	Institute response
NHS Quality Improvement Scotland (continued)	The particular challenge in Scotland is that health professionals and patients have adhered to a standard for some time now, using pemetrexed and cisplatin. Should this NICE ACD which has been developed under the MTA process stands, NHS QIS will be under pressure to withdraw the access of Scottish patients with MPM to this treatment. This is a large group of patients with a very strong lobby. There will be great private and public concern should this take place as a result of a decision made by a health related organization outside of Scotland. *Reviewer 1.* i) Whether you consider that all the relevant evidence has been taken into account. A second RCT of cisplatin plus raltitrexed versus cisplatin reinforces the result of the EMPHACIS trial, although raltitrexed is currently substantially cheaper than pemetrexed (results published in Bottomley A, et al., J Clin Oncol. 2006 Mar 20;24(9):1435-42 and van Meerbeeck JP, et al., J Clin Oncol. 2005 Oct 1;23(28):6881-9.). Astra Zeneca does not seem to want to pursue this indication.	The Committee was aware of this study although it did not form part of the evidence base for this appraisal

Consultee or commentator	Comments	Institute response
NHS Quality Improvement Scotland (continued)	ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate. The main issues revolve around clinical determination of number of cycles used; Lilly will have data on this from their extended access programme (where patients are those we would treat in practice not selected trial participants). Patients not experiencing clinical benefit will rarely go beyond 2 cycles. Given the UK practice in NSCLC, stopping after 4 cycles in all patients will be relatively common. With the tenuous nature of QALY calculations, I suspect that stopping at 2 cycles in those without clinical benefit (>50% from Lilly's own data) and at 4 cycles in all others will bring the cost to less than 30k/QALY. Even going to 6 cycles (of which the last two will be outpatient pemetrexed not inpatient cisplatin-pemetrexed because of neuropathy worries with platinum) in a small number (here the need for the Lilly EAP data) will bring the cost down very close to 30k per QALY. The Lilly EAP data should show patient demography to compare with EMPHACIS (i.e. age, PS, histology, BC), number of cycles given and median survival, which will be a reliable comparison of efficacy with EMPHACIS when prognostic factors are taken into account, and indicate whether the likely fewer number of cycles given off trial do provide similar benefit.	See FAD 4.3.5

Consultee or commentator	Comments	Institute response
NHS Quality Improvement Scotland (continued)	iii) Whether you consider that the provisional recommendations of the Appraisal Committee is sound and constitutes a suitable basis for the preparation of guidance to the NHS. The reality of patient care is that only patients with inoperable (and hence advanced) mesothelioma with either WHO PS 0-1, or at least Karnofsky ≥ 70 will receive chemotherapy, which would meet the "advanced disease good PS" category with more favourable cost per QALY NICE describe. Given that the average number of cycles received will be less than 4 (the half with no clinical benefit stopping at 2, the half with clinical benefit aiming at 6 but some at least not achieving this), the question becomes whether QALY calculated against these costs get under the £30k hurdle. These assumptions may have been included in the calculations made by NICE, but it is not obvious from the guideline. If pemetrexed is turned down, then the alternative regimen will not be MVP or vinorelbine (which I understand MSO1 will confirm) but cisplatin and raltitrexed and comparisons should be made against this regimen.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.

Consultee or commentator	Comments	Institute response
NHS Quality Improvement Scotland (continued)	*Reviewer 2.* We are particularly interested in receiving your comments on the ACD under the following general headings: i) Whether you consider that all the relevant evidence has been taken into account. I do consider that all the relevant evidence has been taken into account. ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate. I do consider that the summaries are a reasonable interpretation of the evidence and implications for NHS appropriate. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. I consider the provisional recommendations sound and a suitable basis for NHS guidance.	No action required

Comments received from website consultation

Commentator	Section of ACD	Comments	Institute response
Relative of a mesothelioma sufferer	Section 1	Having personally witnessed the beneficial effects of this drug on a close relative, I would like to express my utter disgust at the preliminary decision made by NICE to not authorise its use in the treatment of mesothelioma patients. Estimates suggest that it would cost as little as 5 million per year to treat the number of people affected by this terrible disease, and when offset against the costs of providing alternative palliative treatments, will doubtless prove to be cost neutral or even less expensive in the longer term. Prior to receiving pemetrexed disodium, my relative was admitted to hospital 5 times between March and July last year. After receiving the drug, he then went from late July 2006 to last week before he needed to be admitted again. If this is typical, then surely it doesn't take a government "think-tank" to work out the benefits reaped by the NHS in the longer term. We are naturally very bitter as a family at having to watch our loved one suffer and eventually die of such an horrific disease, but this bitterness turns to bewilderment when faced with such abject short-sightedness on the part of NICE especially following so closely on the heels of the Government's recent decision to issue guidelines for the better treatment of meso patients. This country was once rightly proud of its record on treating the sick and infirm - now it is nothing more than a laughing stock for those who are fortunate enough not to need its so-called "services" at this time. Sadly, their laughter will doubtless turn to anguish when their turn comes to experience the failings of such an ailing system made far worse by the decisions of blinkered bureaucrats	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.
Trade Union H&S Officer	Section 1	GMB strongly disagree with this. All sufferers of mesothelioma should be informed of the availability of the drug, its possible benefits and its potential drawbacks and then be allowed to make an informed decision from a personal point of view. As a trade union dealing with the consequences of asbestos exposure over a long time GMB feels that any positive aspect for improvement should not be judged on the basis of cost.	The FAD recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people with advanced disease and good performance status, in whom surgical intervention is considered inappropriate.

Commentator	Section of ACD	Comments	Institute response
Trade Union H&S Officer (continued)	Section 2	Obviously Alimta has been in use for a relatively short period of time and there will have been little opportunity to build up definitive evidence of its" overall benefit. Anecdotal evidence does suggest that in some circumstances there is both a reduction in tumour size, an extension of life and an increase in the quality of that life. This should be investigated further before the drug is threatened by withdrawal.	
	Section 3	Costs per patient are relatively small, particularly bearing in mind the physical suffering involved. The figure of 8,000 for each sufferer will not increase the budget of the NHS by much as there are only a small number of patients every year and this should start to fall in the near future. Care should also be taken that double counting does not take place as these patients would receive some treatment even if the drug was not supplied. Away from the financial costs there is always the issue of morale for victims and their families.	
	Section 4	As stated this is a rare and aggressive malignancy! The overall costs, both now and in the future are very small, with the numbers predicted to diminish after 2010.This should be considered in the light of all the other factors.	
	Section 5	While the role of NICE is important in determining availability of medicines in the future GMB feels that in this area, unlike larger cohorts of sufferers such as breast cancer, the decision to licence the use of Alimta should be taken out of this arena. This is an unusual disease caused by industrial exposure and the period from diagnosis to death is usually relatively small. The numbers who would benefit are also small and the amount of time and resources involved in this is disproportionate to the overall costs. This decision should be taken by the NHS as part of the clinical excellence review (as conducted in January 2007).	
	Section 6	There is no mention of provision as part of treatment in other European or North American countries. Would it be useful to supply these comparisons as part of the consultation exercise?	Cost effectiveness is assessed from an NHS and personal social services perspective
	Section 8	Please see answer to section 5.	