NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Pemetrexed disodium for the treatment of malignant pleural mesothelioma (MPM)

Response to consultee and commentator comments on the ACD

Consultee/ Commentator	Section	Comment	Response
Asbestos Awareness Wales	The evidence	We do not feel that we are qualified to make judgements on the technical evidence but feel that all the relevant evidence has been covered.	Comments noted.
Asbestos Awareness Wales	Clinical effectiveness	It would seem from the evidence reviewed that Pemetrexed combined with Cisplatin is effective in those with advanced disease.	Comments noted.
Asbestos Awareness Wales	Cost effectiveness	Despite the discrepencies and incomplete data in the Appraisal Consultation document (4.3.3) we feel that there is sufficient information already reviewed to suggest significant benefits to patients using the combined regime of Pemetrexed and Cisplatin.	The Committee acknowledged that pemetrexed plus cisplatin has demonstrated survival and quality of life benefits in paragraphs 4.3.2 and 4.3.4 of the FAD.
Asbestos Awareness Wales	Resource impact & implications for the NHS	We consider that the preliminary views on this subject appear to be a reasonable interpretation given the limited evidence available to date. This would seem to be inevitable given that there is no other evaluated study available for MPM comparison.	Comments noted.
Asbestos Awareness Wales	Recommendations	We feel that the evidence to date has been collated and fully appraised by the committee. However, we believe that the NICE proposals to the NHS is premature given the absence of any other suitable chemotherapy regime. It is already well known that inequity exists within the NHS and to restrict the availability of this treatment to trial purposes only is unacceptable. We feel that such an act	The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except as part of new or ongoing clinical trials. "Although respect for autonomy, and individual

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		contavenes the Human Rights and Liberty of already 'compromised' individuals.	choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 11)
Asbestos Awareness Wales	Consideration of the evidence	AAW/UK is concerned that the expert evidence has not been taken into account from the evaluation report when considering the clinical evidence, especially the comments of Dr. Rudd. He states 'that in his view there is sufficient evidence for this drug (pemetrexed) to be recommended as cost effective treatment for Mesothelioma'.	When making its recommendations, the Committee considered all of the evidence contained within the Evaluation Report, including the statements provided by clinical and patient experts (FAD paragraphs 4.3.1 and 4.3.2)
Asbestos Awareness Wales	Recommendations	The late presentation of MPM symptoms is somewhat unique and means that limited life expectancy is the norm. Since there is no standard treatment (2.6) and as stated no standard chemotherapy available for MPM (2.8). Therefore, Pemetrexed plus Cisplatin should be available as a possible treatment for the patient when making informed choices regarding his/her treatment options. In addition to this, in our experience this patient group would value the opportunity to add to the knowledge base of effective and evidence based treatment for MPM.	The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended except as part of new or ongoing clinical trials. "Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 11)
Cancer Backup	Recommendations	The preliminary recommendations state that this technology is recommended only for use as part of ongoing or new clinical trials that compare it with current best practice or other treatments. This decision will effectively mean that the technology remains unavailable to the vast majority of people with mesothelioma.	The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except as part of new or ongoing clinical trials. Paragraph 1.1 of the FAD has been reworded to make this more explicit.

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Cancer Backup	Recommendations	In a phase III study, median survival time was at 12.1 months for pemetrexed and cisplatin, compared to 9.3 months for cisplatin alone. This was a statistically significant difference amongst mesothelioma patients, who currently have very few treatment options available to them. The majority of oncologists in the developed world caring for these patients are already prescribing pemetrexed on the basis of existing evidence. I am concerned, therefore that patients in the UK will not have access to this important treatment which is available to patients in other countries.	The Committee acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD. Nevertheless, it considered that the combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting. The Committee recognised that pemetrexed may be widely used in other countries but still felt that its recommendation was appropriate on the basis of the currently available evidence.
Cancer Backup	Recommendations	It remains the case that pemetrexed is available to patients receiving treatment privately for mesothelioma, but the treatment will not now be offered to NHS patients. This situation will be desperately disappointing for people with mesothelioma, their families and their oncologists. People with mesothelioma are already a relatively disadvantaged group of patients, few of whom will be able to pay for their own treatment.	"In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness" (Social Value Judgements - Principles for the development of NICE guidance; principle 8)
Cancer Backup	Recommendations	I hope that NICE will reconsider its initial decision not to recommend this technology for use in the NHS and that the needs of people with mesothelioma will be fully considered at the next appraisal committee meeting.	Comments noted.
Cancer Research UK	Recommendations	Cancer Research UK does not support NICE's recommendation that the prescription of pemetrexed disodium should be limited to use in the NHS within clinical trials.	Comments noted.
Cancer Research UK	General	We urge the Committee to reconsider the cost effectiveness evaluations on which their recommendations are based, on the grounds that:	Comments noted. See responses to specific points below.

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		• Pemetrexed disodium is the only available and proven treatment for patients with mesothelioma, there is no viable alternative. The effectiveness of MVP and vinorelbine are unproven and thus these regimens are not appropriate comparators from the point of view of the cost analysis; • The cost of supportive care is reduced by giving active chemotherapy contrary to the assumption made in the appraisal; • Quality of life is improved by active chemotherapy not reduced as is the implicit assumption in this appraisal; • There is a good rationale, based on the high expression of folate-receptor alpha in mesothelioma, for why antifolates should be more active than other agents.	
Cancer Research UK	General	Cancer Research UK welcomes the opportunity to respond to this important consultation. We have concerns about a number of inconsistencies and assumptions made throughout the Appraisal Consultation Document. We therefore call on NICE to review and amend this appraisal prior to making their final recommendations.	Comments noted.
Cancer Research UK	Recommendations	The appraisal document recommends pemetrexed disodium for the treatment of malignant pleural mesothelioma only as part of ongoing or new clinical trials that compare it with the current best practice or other promising treatments. Cancer Research UK does not support this recommendation.	Comments noted.
Cancer Research UK	Clinical need & practice	Pemetrexed disodium in combination with cisplatin is the only licensed therapy for the treatment of unresectable malignant pleural mesothelioma in the UK. This treatment has shown a survival advantage in randomised trials and is used throughout the world. Pemetrexed is also regarded as the standard treatment in many areas of the UK where funding for this treatment is made available.	The Committee was aware that pemetrexed plus cisplatin is the only chemotherapy regimen licensed for this indication (FAD paragraph 2.8) and acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust (FAD paragraph 4.3.4). Nevertheless, it considered that the combination was highly unlikely to be cost effective and as

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			such did not feel that its use should be recommended, although it may be used in the context of a clinical trial.
Cancer Research UK	Clinical need & practice	Despite the acknowledgement in Section 2.8 of the appraisal consultation document that pemetrexed in combination with cisplatin is the only chemotherapy regimen currently licensed for this indication, the document states that there is no standard chemotherapy treatment for MPM. While Section 2.6 states that: "there is no standard treatment pathway for MPM in the UK….a patient may receive a combination of treatments", proposals for implementation and audit in Section 7.2 refer to a "current best practice", implying that a current standard treatment regimen is known.	The expression 'standard chemotherapy treatment' refers to alternative therapies that are currently routinely used in the NHS. Pemetrexed plus cisplatin cannot be considered to be standard care simply because it is licensed. Paragraph 7.2 of the FAD has been amended.
Cancer Research UK	Clinical need & practice	The document recognises that extrapleural pneumonectomy is only an option for a very small proportion of patients (1-5%). This procedure carries a very high morbidity is not supported by any clinical trial data and is the subject of the ongoing MARS trial, which has only just started to recruit. It cannot therefore be regarded as a viable treatment option outside the context of this trial.	The Committee felt that it was appropriate to include extrapleural pneumonectomy in the Clinical Need and Practice section of the FAD as this procedure is an option for some, albeit very few, patients. In addition this text highlights the fact that MPM is unresectable in the vast majority of patients.
Cancer Research UK	Clinical need & practice	Section 5.2 in the document refers to MVP (mitomycin C, vinblastine and cisplatin combination) and vinorelbine as "standard care". However, there is no randomised trial evidence to support this claim. In addition: • The major published data supporting the use of MVP are derived from a selected case series collected over 16 years at the Royal Marsden Hospital. 244 patients were seen, 150 selected for treatment and a response rate of 15.3% reported in 131 of these. • There are no published reports of formal Phase II studies reporting radiological response rates.	The expression 'standard care' is used to describe alternative therapies that are currently routinely used in the NHS. The Evaluation Report indicates that vinorelbine and MVP are currently routinely used in the NHS, lack of RCT evidence of their clinical effectiveness nothwithstanding.

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		• All of the reports on MVP come from the same centre and group of collaborators. There are no independent or international trials supporting its activity. • A single Phase II study of vinorelbine conducted in St Bartholomews Hospital published in 2000 reports a radiological response rate of 24% in 29 patients. There are no confirmatory studies of the efficacy of single agent vinorelbine from other centres.	
Cancer Research UK	Clinical need & practice	We also note the statement in Section 2.8 that: "To date there have been no reported randomised controlled trials comparing survival and symptom control in patients receiving chemotherapy with those receiving ASC/BSC." It is our considered view that such trials are no longer relevant following the EMPHACIS study and the EORTC/NCI Canada randomised trial of cisplatin alone, against cisplatin in combination with ralititrexed, in MPM. Both these trials showed a statistically significant survival advantage for the arm treated with the antifolate over those treated with cisplatin alone. If chemotherapy does not increase survival, the only explanation for this result would be that the cisplatin reduced survival compared with best supportive care. However, there are no previous examples of treatment with cisplatin reducing survival. Cisplatin has been shown to increase survival in a large range of cancers (including non-small cell and small cell lung cancer, ovarian cancer, upper GI tumours, breast cancer, and cervical cancer) either in randomised trials or in meta-analyses. Survival of the control arms in the EMPHACIS trial and in the EORTC trial were both better than in historical survival reported for cohorts of mesothelioma patients.	Comments noted. Section 2.8 is a statement of fact. The Committee has not suggested that such trials are appropriate. The Committee acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD.
Cancer Research UK	Evidence & Interpretation	We call on NICE to reconsider the appropriateness of the use of MVP or vinorelbine as a comparator in a cost effectiveness study in the absence of evidence for a clinically beneficial effect, or to	The NICE Guide to the Methods of Technology Appraisal specifies that the comparators used in health technology assessment should be

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		produce evidence to support the use of MVP as a plausible alternative treatment in this appraisal. In their consideration of appropriate comparators with pemetrexed cisplatin the Committee accepts that cisplatin is not commonly used as a single agent in the UK, but in fact the Phase II data to support its use is more extensive than that for MVP. In addition, the toxicities for cisplatin noted in Section 4.3.3 are surpassed by those of MVP, of which cisplatin is itself a component.	"alternative therapies routinely used in the NHS" (page 21). Although cisplatin does not meet this criterion, the Committee considered the estimates of the cost effectiveness of pemetrexed plus cisplatin versus cisplatin alone but observed that these were above conventional cost effectiveness thresholds (FAD paragraphs 4.2.4, 4.2.9 and 4.3.5). The Evaluation Report indicates that vinorelbine and MVP are currently routinely used in the NHS, lack of RCT evidence of their clinical effectiveness and toxicity nothwithstanding.
Cancer Research UK	Evidence & Interpretation	We also disagree with the Committees assumption that BSC/ASC costs would automatically be equivalent in patients receiving and not receiving chemotherapy. There are trials in other types of cancer, including lung and pancreatic cancer that show a reduction in best supportive care costs when cancer chemotherapy is used. Specific chemotherapy inducing a clinical response provides relief of tumour related symptoms. This allows for reduction, or cessation of opiates and other supportive measures, leading to a significant improvement in the quality of life for patients.	Comments noted. The Committee considered that a reduction in the costs of ASC/BSC in patients receiving chemotherapy was very unlikely to be of sufficient magnitude to significantly affect the results of the various cost effectiveness analyses that informed its recommendations.
Cancer Research UK	Research recommendations	We consider the recommendation for trials comparing pemetrexed with MVP is inappropriate, given current paucity of evidence demonstrating that MVP is effective in treating MPM, and bearing in mind that the result of the MSO1 trial should be available soon.	The Committee considered this issue but decided not to change its recommendation.
Cancer Research UK	Scotland	The Scottish Medicines Consortium in July 2005 ruled that pemetrexed in combination with cisplatin is accepted for restricted use within NHS Scotland for the treatment of chemotherapy-naive patients with stage III/VI unresectable malignant pleural mesothelioma. This decision is based on a prolongation of survival with pemetrexed in combination with cisplatin compared with cisplatin alone in patients with unresectable malignant pleural mesothelioma.	The Committee was aware that other bodies had approved the use of pemetrexed but nevertheless considered that its recommendation was appropriate on the basis of the currently available evidence for its clinical and cost effectiveness.

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		It seems incongruous that this decision should be reached in Scotland, and independently by the London Cancer New Drugs Group, but not by NICE in their evaluation.	
Cancer Research UK	Summary	We call on NICE to re-run this appraisal taking into consideration the reduced cost of supportive care following chemotherapy and that there is currently no effective alternative chemotherapy treatment for MPM.	Comments noted. Please see above responses.
Clinical Expert	Clinical effectiveness	It is not mentioned that the evidence for efficacy of pemetrexed is considerably strengthened by similar results in the EORTC trial of raltitrexed, a similar drug. In my view it would be appropriate to make it clearer that the evidence for efficacy of pemetrexed is reasonably good and that it is not being recommended for treatment of NHS mesothelioma patients purely on cost grounds.	The Committee acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD but also noted that there is a lack of evidence demonstrating its superiority to other chemotherapy regimens (FAD paragraph 4.3.11).
Clinical Expert	Cost effectiveness	In considering costs, it is not clear that adequate account has been taken of the likelihood that patients in whom pemetrexed is ineffective, as judged by lack of radiological evidence of tumour response and or lack of clinical benefit, would receive fewer than the hypothesised average of five cycles of therapy, in many cases only two. It is likely that less than half the patients would continue to five or six cycles and these would be the patients who benefited most from it.	FAD amended (paragraphs 4.1.8, 4.2.10, 4.3.8, 4.3.9).
Clinical Expert	Research recommendations	At paragraph 7.2 it is suggested that pemetrexed be used only in clinical trials that compare it with other treatments. At paragraph 4.3.8 and 5.2 it is suggested that future studies should compare pemetrexed with MVP and vinorelbine. Neither regime has yet been shown to increase survival compared with supportive care. If the current BTS MSO-1 study were to demonstrate that either or both regimes does so the median survival advantage is likely to be small, of a similar order of magitude or less than that conferred by pemetrexed plus cisplatin. An equivalence study designed to demonstrate lack of meaningful difference between	Comments noted. The Committee considered that pemetrexed plus cisplatin was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except in the context of a clinical trial.

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		pemetrexed/cisplatin with a median survival advantage of three months and another regime with a similar or shorter median survival advantage would require an unrealistically large number of patients, probably much in excess of 1,000, and it would probably take several years to complete. It is unlikely that many investigators would consider such an exercise worthwhile. Even if they did, it is unlikely that such a study could be funded. If half the patients were randomised to pemetrexed which had not been approved by NICE, other than on the basis of a reference to it being used in clinical trials, it is likely that NHS funding bodies would be reluctant to meet the cost of the drug. The manufacturers of pemetrexed will not do so and it is unlikely that any grant giving body would wish to do so.	
Clinical Expert	Recommendations	While it is reasonable to make an experimental treatment available only within a clinical trial, since it would not otherwise be available to any patients, it is open to question whether it is ethical to determine that standard treatment for a licensed indication shall be available only to NHS patients if they consent to enter a randomised trial. Pemetrexed has been demonstrated in a randomised trial to improve survival and it is licensed for the treatment of mesothelioma. There is no question that it is clinically appropriate treatment for patients who have their own resources. If the position were that pemetrexed would be made available to NHS patients only if they consented to be randomised in a clinical trial this might be construed by ethics committees as inappropriate coercion to enter a randomised trial.	The Committee was aware that pemetrexed plus cisplatin is the only chemotherapy regimen licensed for this indication (FAD paragraph 2.8) and acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust (FAD paragraph 4.3.4). Nevertheless, the Committee's view was that pemetrexed plus cisplatin could not be considered to be standard care simply because it is licensed. It considered that the combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting. The Committee discussed its draft recommendations and decided to reword paragraph 1.1 of the FAD to emphasise that pemetrexed is not recommended, although it may be used in the context of clinical trials.
Clinical Expert	Recommendations /	Future studies likely to be of most interest to investigators and	Comments noted. However, the Committee did

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	Research recommendations	patients are those which will seek to find treatment which will improve survival to a greater extent than does pemetrexed plus platinum. For this purpose trial designs are likely to randomise between what is now regarded in other countries as standard therapy, ie pemetrexed plus platinum, and the same regime plus one or more additional agents, either chemotherapeutic agents or biological agents. If pemetrexed is not approved it is unlikely that any such trials would be possible in the UK because NHS funding bodies are likely to be reluctant to pay for the pemetrexed that would be required in both arms. Hence, far from facilitating future research in treatment of mesothelioma the proposed NICE guidance is likely to hinder it.	not feel that it was appropriate to change its recommendations.
Department of Health	General	The Department of Health have no specific comments to make on the consultation document. However, we have been asked to pass on some comments from a number of clinicians and charities who advise the Department of Health on this condition. I have attached these comments at Annex A but I am sure you will have already received these comments directly.	Comments noted.
Department of Health Advisor	Recommendations	There are few choices in the treatment of mesothelioma and little research has been done to find new treatments. For the first time patients felt that there was some hope of being offered treatment when this came along. The trial results have shown that the use of this drug prolongs life. This may only be by 3-5 months but if the total amount of time left to a person from diagnosis is averaging 9 months then this is an important extra period of time in which much can be achieved.	Comments noted.

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Department of Health Advisor	Recommendations	It is hard to quantify the effect that the "banning" this treatment will have on mesothelioma sufferers and their families but there is real anger among patients and their families about the lack of emphasis placed on the treatment of mesothelioma. This draft guidance, if confirmed by NICE, will only confirm people's fears that they have been forgotten and their lives are of less value than those of people with other cancers which have a higher profile in the media.	Comments noted. The Committee considered evidence from patient groups and took this into account when making its recommendations. "Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 11)
Department of Health Advisor	Consideration of the evidence	The way the draft reads on page 14 para 4.3.7 indicates that performance and improvement is not the key – economics is.	"For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2)
Department of Health Advisor	Recommendations	This is the only licensed treatment for mesothelioma. Whilst it is accepted that the evidence could be better, clinicians who have used the pemetrexed/cisplatin combination in appropriate patients have seen clinical benefit and would want to be able to consider it for the treatment of patients with good performance status but troublesome symptoms.	The Committee acknowledged that pemetrexed plus cisplatin has demonstrated survival and quality of life benefits in paragraphs 4.3.2 and 4.3.4 of the FAD. Nevertheless, it considered that the combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting.
Department of Health Advisor	Consideration of the evidence	Agree that the evidence base for the use of Pemetrexed is far from ideal and that there are no data against best supportive care but that is also true for other chemotherapy regimes in use by many oncologists across the UK.	Comments noted.
Department of Health Advisor	Recommendations	There are no trials including Pemetrexed available to the generality of clinicians in this field in the UK, therefore NICE's conclusion will, in effect, be banning the use of Pemetrexed in mesothelioma in the UK on the NHS unless the Clinical Trials Advisory & Awards	The Committee discussed its draft recommendations and decided to reword paragraph 1.1 of the FAD to emphasise that pemetrexed is not recommended although it may

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		Committee can be persuaded to urgently set up and fund a trial. Even if a trial is established, there will be implications for patients who do not consent to randomisation into a trial and for whom a clinician may consider chemotherapy may be appropriate.	be used in the context of clinical trials. The Committee considered that pemetrexed plus cisplatin was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting.
Department of Health Advisor	Recommendations	Concern that stating that pemetrexed may only be allowed within clinical trials is not ethical (point 1.10 of the Declaration of Helsinki (1964):'When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in dependent relationship to him or her or may consent under duress.....'). If patients are aware that the only way of receiving the licensed therapy for their disease is within a trial, one might consider that the NICE guidance comes close to introducing 'consent under duress'.	The Committee discussed its draft recommendations and decided to reword paragraph 1.1 of the FAD to emphasise that pemetrexed is not recommended although it may be used in the context of clinical trials. The Committee considered that pemetrexed plus cisplatin was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting.
Department of Health Advisor	Recommendations	Plea for NICE to recommend that, wherever possible, patients should receive chemotherapy for mesothelioma in the context of a clinical trial, but that consideration can also be given to prescribing pemetrexed (by a specialist oncologist) where a trial is not available or where a patient does not consent to take part in a trial but has good performance status (status 0 and 1).	The Committee considered that pemetrexed plus cisplatin was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting.
Eli Lilly	Consideration of the evidence	**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.	Comments noted.

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		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.	
Eli Lilly	Cost effectiveness	**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 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.	Comments noted, see FAD paragraphs 4.1.8, 4.2.10, 4.3.9.

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		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%). 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. [TL note – for supporting tables please refer to original document]	
Eli Lilly	Consideration of the evidence	**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	The NICE 'Guide to the Methods of Health Technology Appraisal' stipulates that the QALY should be used to value health effects in economic analyses submitted to the Institute. In the past, the Institute has made several recommendations on the basis of life years gained (LYG) but generally these appraisals took place before the introduction of the NICE Methods Guide (April 2004) which specifies the use of the QALY. More recently, LYGs have only been considered, at the discretion of the Appraisal Committee, in exceptional circumstances (for example where no quality of life data was available or where an intervention has wider societal benefits which could not easily be captured within a QALY).

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		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.	In its paper 'Social Value Judgements - Principles for the development of NICE guidance', the Citizens' Council indicates [emphasis added] that "in ***some*** instances 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". It is anticipated that these instances would reflect the criteria given above. It does not follow that, if the Committee were to consider an alternative measure of health benefit, the suggested acceptability thresholds based on the QALY would be the same. See NICE Guide to the Methods of Technology Appraisal, paragraph 6.2.6.12.
Eli Lilly	Consideration of the evidence	**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 cost-effectiveness analysis, it is generally accepted that mean treatment effects should be used, as they describe the expected treatment effect for each patient. Median survival is generally considered to be an inappropriate measure of effectiveness for the purpose of economic analysis. This is because survival times are known to be skewed and the median is likely to underestimate survival by not taking into account the survival of those patients who live significantly longer than most. The Committee did not feel that it was appropriate to consider median survival estimates in view of the above.

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		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.	
Eli Lilly	Consideration of the evidence	**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	See above responses. The Committee took these factors into account when making its recommendations (see FAD paragraphs 4.3.2 and 4.3.11).

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		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.	
Eli Lilly	Clinical need & practice	**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.	Paragraph 4.2.2 amended in FAD. Comments noted. It is stated in paragraph 2.7 of the FAD that "treatment…often does not involve treating the tumour with chemotherapy".

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		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. [TL note – for supporting tables please refer to original document]	Paragraph 5.2 amended in FAD (now 6.2) Comments noted. The Committee stated that the results of the MS01 trial "would be extremely important in determining the effectiveness of [MVP and vinorelbine]".
Eli Lilly	Consideration of the evidence	**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,	The Committee found the indirect comparison provided by Lilly's model 2 helpful and took its results into account when making its recommendations. However, it felt that the costs of comparator treatments may have been overestimated (and survival underestimated) and was therefore not convinced that pemetrexed was likely to be cost effective versus MVP, vinorelbine or ASC/BSC (see FAD paragraph 4.3.6).

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		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.	
Eli Lilly	Consideration of the evidence	**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).	Comments noted. Paragraph 4.3.3 of FAD amended accordingly.

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		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	

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		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.	
Eli Lilly	Clinical need and practice	**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	Comments noted. The Committee acknowledged that pemetrexed is valued as a treatment option by patients and clinicians (see FAD paragraph 4.3.2).

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		'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.	
Eli Lilly	NHS Resource Impact	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.	Comments noted. The Committee does not consider the affordability of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).

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Eli Lilly	Consideration of the evidence	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.	Comments noted.
Eli Lilly	Consideration of the evidence / cost effectiveness	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.	Comments noted. FAD amended accordingly (paragraphs 4.1.8, 4.2.10, 4.3.8, 4.3.9).
Eli Lilly	Consideration of the evidence	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.	The Committee has acknowledged the lack of evidence for comparator treatments (see FAD paragraphs 4.3.3, 4.3.6, 4.3.11).
Eli Lilly	Consideration of the evidence	Furthermore, MPM is a devastating disease, invariably associated with a fatal outcome and associated with particularly distressing	The Committee has taken the clinical need of MPM patients into account in formulating its

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		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.	recommendations (see FAD section 2 and paragraphs 4.3.2 and 4.3.11).
Eli Lilly	Consideration of the evidence	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.	Paragraph 4.3.2 of the FAD acknowledges that patients value pemetrexed as a treatment option. "Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 11).
Eli Lilly	Consideration of the evidence	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.	See responses to above comments.
Eli Lilly	Cost effectiveness	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.	See responses to above comments.
Eli Lilly	Consideration of the evidence	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	See responses to above comments.

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		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.	
June Hancock Mesothelioma Research Fund	The evidence	JHMRF is satisfied that all the relevant evidence available was included in the report. The systematic review covered not only published reports and scrutiny of the reference lists of retrieved articles but also used internet searches to find details of ongoing clinical trials and other "grey literature" reports, as well as hand searches of documents from relevant conference proceedings. The list of consultees invited to contribute to the evidence was comprehensive and included patients' and carers' perspectives.	Comments noted.
June Hancock Mesothelioma Research Fund	Clinical & cost effectiveness / research recommendations	Given the paucity of scientific evidence available for comparison, JHMRF consider that the summaries of clinical and cost effectiveness were fair. The Assessment Group only identified one Phase III randomised controlled trial of pemetrexed disodium, the EMPHACIS Study, the results of which formed the basis for the assessment of the clinical effectiveness of pemetrexed. Notwithstanding that this evidence was sufficient for the granting of a licence for the use of pemetrexed disodium, JHMRF feel that there are still considerable gaps in knowledge about the benefit of pemetrexed disodium compared to other (less costly) chemotherapy regimens. Moreover there is still little evidence that any single agent or combination chemotherapy offers a survival advantage to patients when compared to best supportive or active supportive care. While the results of the MS01 trial will go some way to answering this question, we would urge NICE to recommend that further trials of pemetrexed disodium and other chemotherapy agents are necessary to provide additional evidence.	Comments noted. Such trials are recommended in paragraph 6.2 of the FAD.
June Hancock	Recommendations	There is no conclusive evidence that provides a sound clinical basis	Comments noted. The Committee considered

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Mesothelioma Research Fund		on which to recommend that the NHS should provide pemetrexed disodium as a treatment option for malignant pleural mesothelioma, and the economic evaluation has shown that the cost implications of pemetrexed are high. In view of this finding the provisional recommendations appear reasonable. However, in consideration of the fact that mesothelioma is a terminal disease that is acquired principally by occupational exposure, and for which few treatment options are available, JHMRF request that NICE give consideration to changing their recommendation to the NHS to allow the continued use of pemetrexed until the results of the MS01 trial are known. As the manufacturers (Lilly) have no plans for further clinical trials of pemetrexed in the UK, this will ensure that patients are not disadvantaged by limiting access to pemetrexed to clinical trial settings alone.	that pemetrexed plus cisplatin was highly unlikely to be cost effective and as such did not feel that its use should be recommended outside of a clinical trial setting. In view of this, the Committee did not feel that it was appropriate to defer the publication of guidance.
June Hancock Mesothelioma Research Fund	Review date	With regard to the date set for review of the NICE recommendations: Recruitment to the MS01 trial has been slower than predicted and it is not expected that the required sample size will be achieved before summer 2006. This will delay the analysis and publication of results. Consequently, although an earlier review would be desirable, the proposed date of May 2008 seems to be a realistic in order to ensure that the results of MS01 can be taken into consideration.	Comments noted.
June Hancock Mesothelioma Research Fund	Research recommendations – quality of life	In addition, JHMRF would like to submit that in view of the considerable impact that treatment with platinum-based and other combination chemotherapy regimens can have on quality of life for patients more needs to be known about the trade-off patients are prepared to make between the toxic effects of treatment and potential outcomes. JHMRF consider that studies are needed specifically to address this issue for patients with malignant mesothelioma. Participants in the EMPHACIS trial, for example, were undergoing a relatively lengthy (median 15 week) treatment to gain a moderately small (around 12 week) improvement in survival. We would therefore urge NICE to recommend that studies into this	Comments noted. The Committee did not feel that it was appropriate to include a research recommendation as suggested.

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		aspect of patient choice are commissioned.	
June Hancock Mesothelioma Research Fund	Evaluation report	JHMRF would also suggest that NICE give careful consideration to the production of a lay summary that will interpret the results of the Evaluation Report in a format that is accessible to, and understood by, service users. This is particularly important in view of the recent press and media coverage of the preliminary findings of the NICE review, and the specific circumstances of the patient group that it will need to address.	Comments noted. A guide for patients, carers and the public will be available when the final guidance is published.
MRC Clinical Trials Unit	General	I think in this instance there is nothing we can add to the discussion, and therefore we will not be returning any formal comments.	Comments noted.
NHS QIS (1)	Cost effectiveness	I think it has but the economic model used is flawed. They should not have used a BSA of 2.0m2 to perform the pharmaco economic analyses. Also it assumes that patients will get 5 cycles of pemetrexed and cisplatin. This would be unusual in UK practice. In West of Scotland no patient receives more than 4 cycles.	The economic model does not use a BSA of $2.0m^2$. Nor does it assume that all patients will receive 5 cycles of treatment. The model is based on individual patient data from the EMPHACIS trial (see FAD paragraph 4.2.3). The Committee considered the possibility that patients may receive fewer cycles in clinical practice (see FAD paragraph 4.3.8).
NHS QIS (1)	Cost effectiveness	I think the summary is accurate but I think the QALY calculations will be flawed because of the above.	See above response.
NHS QIS (1)	Cost effectiveness	Only if the cost modelling is changed. The trials demonstrate a survival and QOL advantage in a disease for which there is no other systemic therapy. There will be an outcry from patient groups. Also the SMC have approved this drug in combination. NICE guidance will supercede SMC so it will be withdrawn. This will be a huge political issue.	Comments noted.
NHS QIS (2)	Evidence & interpretation	Yes , I consider all relevant evidence has been considered.	Comments noted.
NHS QIS (2)	Consideration of the evidence	By coincidence I recently refereed a paper [bjc] relating to a cost /effectiveness model for Pemetrexed in MPM. I agree with the comments paragraph 4.3.6 regarding the high degree of uncertainty surrounding the assumptions underpinning the model.	Comments noted.

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NHS QIS (4)	Recommendations	This ACD concludes that pemetrexed is not cost effective in the treatment of mesothelioma. Only one randomised trial has compared pemetrexed with platinum versus platinum alone, and while there may be reservations about the appropriateness of single-agent platinum as a control, there was only a survival advantage of three months. Treatment lasted an average of 18 weeks to gain this three month advantage, and symptom control and quality of life measures were also said to be statistically superior. Although statistically significant, I would doubt the clinical significance of prolonging death in this extremely unpleasant cancer. Given the costs of the drug, the cost effectiveness was unsurprisingly high, and I am quite certain that the right conclusion is that this agent should not be used outside clinical trials unless or until appropriately designed clinical trials have verified its utility.	Comments noted.
OEDA	General	Having studied [the documents] carefully, I am sending you a copy of OEDA's comments, e.mailed 7 February 2006 to Cathryn Fuller.	Comments noted.
OEDA	General	The prediction that mesothelioma would not occur after the year 2000 has proved false. Patients are distressed if told no treatment is available; morale improves if treatment is offered. But pemetrexed therapy is suitable for only a relatively small number of MPM patients. Research and funding to find and provide effective treatment for all mesothelioma patients is needed urgently.	Comments noted.
OEDA	General (refers to the Assessment Report)l	Randomised controlled clinical trials may be regarded as essential for assessing clinical efficacy of new drugs but are not appropriate for mesothelioma patients whose life expectancy is so short that they need to make an informed choice; do they want treatment? If so the benefits and toxicities of treatments available should be explained to them. The choice should be theirs. LRLG appears to share this view, They conclude: Any decision to use pemetrexed plus cisplatin in an individual patient needs to be in full collaboration with that patient, against a background of high quality palliative care services. The patient	Comments noted.

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		needs to be well informed of the benefits and toxicities of the regimen. Much more research is needed into the optimum chemotherapy for these patients, and a clear definition of what constitutes best supportive care. (page 86)	
OEDA	Clinical Effectiveness	Survival time for those treated with pemetrexed plus cisplatin is not significantly longer than that of those who receive no chemotherapy. Quality of life may be poor: it is recognised that when pemetrexed is used the incidence of severe toxicity is high. (page 85)	Comments noted.
OEDA	Clinical Effectiveness	Quality of life is important. I am concerned that I have been able to obtain only limited information on the criteria to be used when assessing Quality of Life. It appears that it is often ignored or only poorly assessed.	Comments noted.
OEDA	Recommendations (refers to the Assessment Report)	The cost of pemetrexed is high. I agree with the Eli Lilly conclusion that pemetrexed plus cisplatin does not fall within the conventional range of cost-effectiveness. While they believe that the therapy should be given special consideration owing to the lack of any other proven alternative to supportive care, I feel that there should in addition be funding to find treatment that will benefit all mesothelioma patients. For example, early diagnosis would benefit all.	Comments noted.
OEDA	Clinical effectiveness (refers to the Assessment Report)	I am concerned to read that Eli Lilly has granted to the Assessment Group only limited access to selected individual patient date (IPD) (page 75). I find this worrying and unacceptable.	Comments noted.
OEDA	General (refers to the Assessment Report)	There is a suggestion that costs would be cut if pemetrexed were to be made available in smaller vials, yet 100 mg vials will not be available until 2008 or later (page 75). This seems to be unreasonably delayed. Can Eli Lilly not make other additional cost savings?	Comments noted.
OEDA	Clinical effectiveness (refers to the Assessment Report)	The assessors recognise (page 23) that because this was a single blind trial, bias may have been introduced.	Comments noted.
OEDA	General	How many more patients have refused to participate in pemetrexed	Comments noted.

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		trials when told that they could be 'randomly' i.e. arbitrarily allocated to a group denied any treatment?	
RCN	Recommendations	We are very disappointed with the preliminary recommendations of the Appraisal Committee regarding pemetrexed.	Comments noted.
RCN	General	The arrival and licensing of pemetrexed offered a glimmer of hope for Mesothelioma patients in that it may pave the way for more trials and more drugs to follow to add to the weak evidence base currently underpinning chemotherapy treatment in Mesothelioma.	Comments noted.
RCN	Recommendations	Mesothelioma patients experience poor survival often regardless of what treatment they receive, they enter into treatment with the aim of minimizing or avoiding nasty symptoms for as long as it is possible. They do not survive long enough or have the strength to have their voice heard in the manner that breast cancer patients do. This decision adds almost unbearably to the injustice that they are already subjected to.	Comments noted. The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except as part of new or ongoing clinical trials. The Committee considered evidence submitted by patient groups (FAD paragraphs 4.3.1 and 4.3.2).
RCN	Research recommendations	We are not aware of any trials currently involved nationally using pemetrexed and planning such a trial, getting it though ethics and designing a trial suitable for all patients is an enormous lengthy task. Granted pemetrexed does not hold all the answers for all Mesothelioma patients but it offers an evidence based option for some and it is our view that cancer experts should be afforded the option to use their clinical judgment to prescribe it where they and their patients consider it appropriate.	Comments noted. The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except as part of new or ongoing clinical trials.
RCN	Recommendations	We would urge the Committee to reconsider its recommendations.	Comments noted.
RPSGB	General	Please note that the Royal Pharmaceutical Society of Great Britain will not be commenting on the above consultation.	Comments noted.

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NHS Professional 1	Recommendations	Does the recommendation by the Appraisal Committee indicate that PCTs should fund the pemetrexed cost for the randomised clinical trials proposed by the Committee in section 4.3.8?	This is outside the Committee's remit.
NHS Professional 1	Clinical need & practice	2.5 Surgical intervention is not required for the staging of the vast majority of patients who are clearly beyond surgical intervention based on clinical evaluation, CT scans etc.	Comments noted. Sentence added to paragraph 2.5 of the FAD.
NHS Professional 1	Clinical need & practice	2.6 There are standard treatment pathways perhaps not universally in the UK but in the high incidence areas were expertise exists, e.g. decision as to whether the patient is resectable/operable or not, if not, depending on performance status (PS 0, 1 equivalent to KP 70 and above) is the patient suitable for chemotherapy including the only licensed combination pemetrexed with cisplatin?	Comments noted. Having taking into account the evidence in the Evaluation Report and the views of the clinical experts, the Committee did not feel that it was appropriate to amend the FAD as the guidance is applicable throughout England and Wales and must therefore attempt to reflect the general situation.
NHS Professional 1	Clinical need & practice	2.7 Chemotherapy can be recommended for patients with good performance status (see above) and if the patient so desires chemotherapy. What is the meaning of "often"? The specific treatment depends largely on whom the patient sees i.e. an expert in mesothelioma systemic treatment or not, in the latter case they are more likely to receive only symptom control.	Comments noted. The Committee did not feel that the text in 2.7 was inaccurate and as such no amendments were made.
NHS Professional 1	Clinical need & practice	2.8 There is a standard chemotherapy now the only one licensed pemetrexed cisplatin widely used in the EU but less so in England and Wales. Our country's poorer cancer survivals are now linked with the lack and slower uptake of new drugs in England and Wales due to NICE (Wilking and Jonsson Karolinska report 2005). The MVP and vinorelbine data are limited TO only a few patients (see table below) [TL note: please refer to original document for table] compared with the very large pivotal trial of pemetrexed cisplatin versus cisplatin alone. Given the RCT size and the poorer grade of data on MVP vinorelbine, it is much more certain that pemetrexed cisplatin is better than cisplatin alone. The uncertainty resides more in the benefit, if any, of MVP, active supportive care	Comments noted.

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		or weekly vinorelbine. Furthermore, there is another RCT albeit rather small (not mentioned) that did indicate a trend to survival improvement and extended period of symptom control with early MVP versus delayed MVP [O'Brien Annals of Oncology 2006, 270-275]. In the MESO 1 trial which is frequently commented on favourably, some patients in the active supportive care arm will, of course, receive chemotherapy. MESO 1 is unlikely to show any difference given the drugs being used, the trial design , collapsing of the two chemotherapy arms into one etc.It is therefore unfair that the appraisal document continually portrays MESO 1 trial in such favourable light and it's use as an argument for delaying /preventing the more general use pemetrexed.	The results of this RCT were published after the deadline for the submission of evidence for this appraisal. Comments noted, however the Committee still felt that the results of the MESO1 trial will be important in determining the effectiveness of chemotherapy in MPM (see FAD paragraph 4.3.11).
NHS Professional 1	Clinical effectiveness	4.1.1 As mentioned previously, there is a second RCT [O'Brien et al] using MVP immediate versus delayed.	The results of this RCT were published after the deadline for the submission of evidence for this appraisal.
NHS Professional 1	Clinical effectiveness	4.1.8 The large Emphasis Trial did not just suggest – it demonstrated a significant survival benefit for pemetrexate cisplatin.	The word "suggest" is used because this sentence refers to the possible effect of pemetrexed in the general patient population and not to the effects that were observed in the trial.
NHS Professional 1		4.2.7 It is not clear where the Assessment Group obtained the survival estimate for MVP and performance status ,was this from the single institution study over 16 years (Andreopoulou et al Annals Oncol 2004),hardly a reliable base for such a strong appraisal conclusion. There may have been an error in translating Karnofsky Performance Score [Vogelzang et al J Clin Oncol 2003] into PS 0/1, 2. Karnofsky Performance 70 is equivalent to a PS2 – this should be checked. Furthermore, the source of the survival estimate for ASC taken from a meta-analysis is not given to check validity. If this was the Herndon (Chest 1998) prognostic analysis ,then age and white blood cell count were also important cofactors,	Please refer to the Addendum to the Assessment Report (*http://www.nice.org.uk/page.aspx?o=299861*) and to the additional work undertaken by the NICE Technical Lead (*http://www.nice.org.uk/page.aspx?o=299844*) for clarification of the sources of the efficacy data used in the model. The Committee recognised that the efficacy assumptions underpinning the indirect

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		is not clear how performance status alone could be separated out [Chest 1998; 113:723-31.If it was the Andreopoulou et al Annals Oncol 2004 paper of only 43 patients these were treated with MVP +/_other drugs and in the multivariate analysis PS was not an independent factor when pathology was included. There are therefore great reservations about the assumptions and accuracy of Section 4.2.7.	comparison were subject to a high degree of uncertainty and were therefore cautious in interpreting these (FAD paragraph 4.3.6). Nevertheless, they thought that it was appropriate to consider the estimates of the cost effectiveness of pemetrexed versus MVP, vinorelbine, and ASC/BSC, given that the comparator used in the main cost effectiveness analysis (cisplatin) is not routinely used in the NHS.
NHS Professional 1	Cost effectiveness	4.2.10 As regards the summary of the evidence on cost effective 4.2.0, the very high values quoted are widely different from the values quoted in the publication from the Regional Drugs and Therapeutics Centre in Newcastle on the use of pemetrexed (February 2006) see page 11 where the total cost LYG is £23,272 exclusive of VAT and when the audit from my own hospital was used, the estimate cost per LYG was £16,340 when compared to cisplatin alone which is entirely comparable with the cost per LYG of other interventions approved by NICE for the treatment of non-small cell lung cancer. Furthermore, the Scottish Medicines Consortium gave an incremental cost per life year saved of £20,284based on a survival gain of 4.8 months in those fully supplemented patients with advanced disease. Therefore, the whole cost effectiveness section is controversial, more realistic and clinically relevant data should be incorporated.	The NICE 'Guide to the Methods of Health Technology Appraisal' stipulates that the QALY should be used to value health effects in economic analyses submitted to the Institute. In the past, the Institute has made several recommendations on the basis of life years gained (LYG) but generally these appraisals took place before the introduction of the NICE Methods Guide (April 2004) which specifies the use of the QALY. More recently, LYGs have only been considered, at the discretion of the Appraisal Committee, in exceptional circumstances (for example where no quality of life data was available or where an intervention has wider societal benefits which could not easily be captured within a QALY). It does not follow that, if the Committee were to consider an alternative measure of health benefit, the suggested acceptability thresholds based on the QALY would be the same. "The Committee has a strong preference for

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			expressing health gains in terms of QALYs. In circumstances where the health gain is expressed in terms of life-years gained, the range of most plausible ICERs that are acceptable will be substantially lower than those described above. The exact adjustment that the Committee considers should be made to take account of the differences between QALYs and life-years gained are guided by reference to the population norms for HRQL for the affected population, and generally lower than this for a sick population." NICE Guide to the Methods of Technology Appraisal, paragraph 6.2.6.12.
NHS Professional 1	Cost effectiveness	4.2.9 When was it decided that the maximum acceptable ICER was £30,000 per QALY and who authorised this value?	Please refer to the NICE 'Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.10 and 6.2.6.11.
NHS Professional 1	Consideration of the evidence	4.3.3 Concerning cisplatin as a reasonable standard, this was decided by the United States FDA given the information on a variety of single agents. Furthermore, NICE accepted single agent cisplatin as a valid comparator against paclitaxel, gemcitabine, vinorelbine in the appraisal of non-small cell lung cancer drugs. It is unclear therefore why the Committee thought cisplatin was not a reasonable standard in the EMPHACIS trial. Certainly it performs just as well as the other drugs including vinorelbine (smaller database) and MVP see Table. Also it is important to note that the MVP database on so-called quality of life was physician rated and unvalidated. The dose of cisplatin is a standard dose, if a lower dose had been used then it would have been criticised as inflating the survival benefit with pemetrexed! Moreover the cisplatin dose used was determined from the phase I/II work with pemetrexed (Thodtmann et al J Clin Oncol 1999) There is then more validity for the cisplatin	Comments noted. The Committee acknowledges that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD.

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		dose as a singe agent than an ad hoc lower dose or some other drug(s) as a comparator argued for by the Committee.	
NHS Professional 1	Consideration of the evidence	4.3.3 Concern should be registered that the manufacturer had not sanctioned its use. It would be difficult to see how the manufacturer could make the drug available within an ongoing trial over which it had no control, legally or otherwise. I have never been able to insert an unlicensed product into a Government run research trial. Another element is the membership of the Clinical Expert Committee and the June Hancock Mesothelioma Research Fund, all of whom are Principal Investigator, Clinical Coordinators or sponsors of the MESO 1 trial which has been heavily used by the Appraisal Committee as an argument against the non trial use of pemetrexed.	Paragraph 4.3.3 amended accordingly. Comments noted. The Committee did not consider that it has overstated the value of the MS01 trial.
NHS Professional 1	Consideration of the evidence	4.3.4 The argument that cisplatin could not be considered to be an equivalent to placebo or ASC/BSC because of adverse effects is the old argument against the use of chemotherapy in non-small cell lung cancer which was disproved. Although chemotherapy may have transient side effects ,in general it has been shown to improve overall quality of life and there is no reason why this will be different in malignant mesothelioma (see above) as was demonstrated in the NICE Appraisal Document on Chemotherapy in Non-Small Cell Lung Cancer. Chemotherapy also (despite the Committee's comment and cost assumptions) actually reduces time in terminal care and days in hospital/hospice!	Comments noted.
NHS Professional 1	Consideration of the evidence	4.3.5 Concerning the fact that the study populations were unlikely to be comparable, particularly in terms of performance status, this is not clear when one actually inspects the data table!	Having considered the Addendum to the Assessment Report, the Committee felt that its assessment was reasonable.
NHS Professional 1	Consideration of the evidence	4.3.7 Please see other comments re stage and PS as a rebuttal that the economic analysis did not support a recommendation.	This issue was discussed by the Committee and paragraph 4.3.10 amended.
NHS Professional 1	General	In general the preliminary appraisal was somewhat uninformed with a singular, particular view being promoted, particularly favourable to	The Committee did not consider that it has overstated the value of the MS01 trial.

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		the MESO 1 trial which will deprive patients of the marked survival and quality of life benefits already observed in the large randomised clinical trial of pemetrexate, cisplatin versus cisplatin alone.	
NHS Professional 1	General	My own experience with pemetrexed plus cisplatin and that of colleagues with experience in the non trial use is that it is an extremely useful combination with low toxicity producing improvement in the patient's wellbeing confirmed by our own audit data which demonstrates that the combination is behaving in practice as it did in the trial context.	Comments noted.
NHS Professional 2	General	Does age make any difference to the cost effectiveness or the recommendation. We recently had this requested for a relatively young patient of 38 with inoperable mesothelioma. Is there any evidence that younger patients respond any better or that the QALY is any different.	No subgroup analysis by age was submitted the Institute for this appraisal. Some information about prognostic factors in MPM can be found in the Assessment Report (*http://www.nice.org.uk/page.aspx?o=300055*).
NHS Professional 3	Recommendations	Strongly support this approach. Do not consider current evidence of effectiveness and cost effectiveness is sufficient to support recommendation of routine use in NHS.	Comments noted.
NHS Professional 3	Clinical need & practice	Clear statement of current position. Fully support this.	Comments noted.
NHS Professional 3	The technology	GOod summary of current position.	Comments noted.
NHS Professional 3	Clinical and cost effectiveness	Fair summary of current evidence.	Comments noted.
NHS Professional 3	Research recommendations	Fully support these.	Comments noted.
NHS Professional 3	Resource impact	Costing templates are extremely helpful	Comments noted.
NHS Professional 3	Implementation & audit	Support these proposals.	Comments noted.
NHS Professional 4	Recommendations	I feel there is already enough evidence to show that premetrexed is an active drug in the treatment of mesothelioma. Additionally there is enough evidence to say that it is better tolerated than other platinum containing regimens such as MVP. This latter issue is a	The Committee acknowledges that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD. The economic analysis includes the

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		key point. Has your analysis taking into account the cost to the NHS of looking after all the neutropenic sepsis generated by use of non premetrexed combinations?	costs of adverse events in both pemetrexed and comparator treatments (for further details please refer to the Assessment Report *http://www.nice.org.uk/page.aspx?o=300055*)
NHS Professional 4	Clinical need & practice	If premetrexed + cisplatin is the only lisenced regimen for mesothelioma, then by definition all other regimens in use today are not lisenced. Therefore you seem to be advocating the use of unlisenced medication to treat a disease. This is at odds with the policy of adjuvant herceptin where a major argument for not giving it NICE approval was the fact that it is not lisenced.	The Appraisal Committee does not make recommendations in respect of comparator treatments.
NHS Professional 4	The technology	You overstate the toxicities of premetrexed here. Generally with adequate B12/folate supplementation side effects are minimal compared to most other conventional cytotoxic agents in current use.	The toxicities of pemetrexed are taken from the Summary of Product Characteristics.
NHS Professional 4	Clinical and cost effectiveness	Patients generally are self selecting. By this I mean that many will not be fit for chemotherapy and will go straight to palliative care. Only the fit patients will be considered for chemotherapy. All of these fit patients are likely to get a multiagent combination chemotherapy regimen (usually MVP). Therefore the most appropriate analysis is comparing cost of MVP vs CisAlimta. There is no argument for comparing BSC to CisAlimta for fit patients as this group are all highly likely to get chemotherapy within current NHS practice	Comments noted. However, having considered the evidence made available to it and the lack of standard treatment pathway for MPM patients, the Committee felt that it was possible that not all patients with good performance status would receive chemotherapy. The Committee concluded that pemetrexed plus cisplatin was unlikely to be cost effective against any of the comparators considered.
NHS Professional 4	Research recommendations	To compare CisAlimta to MVP in a randomised clinical trial, we would have to wait another 5-6 years at least. Our patients need answers sooner. If CisAlimta is not to be NICE approved can NICE comment on what it think the standard of care should be for the treatment of this disease?	The scope of this appraisal is to consider the clinical and cost effectiveness of pemetrexed for the treatment of MPM. It is outside the scope of this appraisal to make recommendations about what standard care should be.
NHS Professional 5	Recommendations	The UK Specialised Services Public Health Network fully endorse the recommendations. We particularly support the recommendation which requires further research to be done - and in particular that the specific recommendation is that this should involve comparing outcome with current practice. We view this as both ethical and a	Comments noted.

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		means to provide the best information. Even if the QALY for this treatment had been much lower - this group would question the funding priority that a treatment largely extending life by 3 months should receive given the other demands on the NHS. It is worth perhaps noting that in a recent priority setting pilot exercise - using real service developments bids) both clinicians and patient representatives generally gave lower priority to new technologies compared to improving the quality of existing clinical services. Treatments such as this raise a more basic question concerning what clinical outcomes should the NHS be investing in regardless of QALY calculations.	
NHS Professional 6	Recommendations	As someone invovled in the actual treatment of patients with mesothelioma, I find your final recommendation at odds with the rest of the report. The combination of Alimta and Cisplatin is the only chemotherapy treatment to have been shown in a randomized trial to produce a survival advantage in this tumour type. It has also been shown to produce a quality of life improvement with regards to the distressing symptoms of mesothelioma. Having had practical experience of using these drugs I can confirm that the trial results are reproducible in the ""real World"". The combination has been widely accepted as the standard of care in Europe and America. Yet again we lag behind in the UK, awaiting, on your recommendation, further studies, which, in view of the rarity of the condition, will be difficult and time-consuming to perform.	The Committee acknowledged that pemetrexed plus cisplatin has demonstrated survival and quality of life benefits in paragraphs 4.3.2 and 4.3.4 of the FAD. The Committee recognised that pemetrexed may be widely used in other countries but still feels that its recommendation is appropriate on the basis of the currently available evidence. The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended, except as part of new or ongoing clinical trials.
NHS Professional 7	Recommendations	Not all patients wish to enter clinical trials, pemetrexed is the only drug licensed in MPM. The EMPHACIS trial demonstrated an extremely large increase in median survival (4.8months) in a very resistant form of cancer	The Committee acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD. The Committee considered that the pemetrexed plus cisplatin combination was highly unlikely to be cost effective and as such did not feel that its use should be recommended,

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			except as part of new or ongoing clinical trials. The Committee discussed its draft recommendations and decided to reword paragraph 1.1 of the FAD to emphasise that pemetrexed is not recommended although it may be used in the context of clinical trials.
NHS Professional 7	Clinical need & practice	Patients with good performance status were offered chemotherapy usually cisplatinum combination eg MVP. There is a randomised controlled trial which indicates benefit from early v delayed chemotherapy (O Brien et al Annals of Oncology 2006, 270-275) where early chemo provided extended symptom control and trend to survival advantage of MVP.	The results of this RCT were published after the deadline for the submission of evidence for this appraisal.
NHS Professional 7	Clinical & cost effectiveness	4.1.8 Results from EMPHACIS demonstrated a highly statistically significant survival benefit. 4.2.9 Who has decided the maximum acceptable ICER of 30,000 per QALY? 4.3.3 MSO1 was ongoing, how could the manufacturer have inserted their drug into a MRC trial? 4.3.4 Comment that cisplatin higher cost than placebo/BSC unfounded in literature 4.3.6 Survival benefit demonstrated with pemetrexed, why is this not cost effective compared to MVP etc where no survival benefit has been demonstrated 4.3.7 why does the committee conclude recommendation based on stage not workable? what is relevant is whether the tumour is operable or not and this can be determined in onc centres.	4.1.8 The Committee acknowledged that the survival benefit demonstrated by pemetrexed plus cisplatin is likely to be robust in paragraph 4.3.4 of the FAD; 4.2.9 Please refer to the NICE 'Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.10 and 6.2.6.11. 4.3.3 Text amended accordingly; 4.3.4 The Committee considered that a reduction in the costs of ASC/BSC in patients receiving chemotherapy was very unlikely to be of sufficient magnitude to significantly affect the results of the various cost effectiveness analyses that informed its recommendations; 4.3.6 cost effectiveness analysis takes into account the costs of technologies as well as their effectiveness; 4.3.7 This issue was discussed by the Committee and paragraph 4.3.10 amended accordingly. A sentence was also added to paragraph 2.5.
NHS Professional 7	Research recommendations	5.2 The Committee states that MVP and vinorelbine is current standard care, it is not and remains unproven. Committee stated	The expression 'standard care' means alternative therapies that are currently routinely

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		earlier that BSC was standard.	used in the NHS. The Evaluation Report indicates that vinorelbine and MVP and ASC/BSC are currently routinely used in the NHS, lack of RCT evidence of their clinical effectiveness nothwithstanding.
TUC	Recommendations	I am writing on behalf of the TUC to express our grave concern over the preliminary guidance from the National Institute for Health and Clinical Excellence on Alimta.	Comments noted.
TUC	Clinical need & practice / clinical effectiveness	We have, for some time, been aware of the significant geographical variation in the availability of this treatment for mesothelioma. We have also had very positive accounts of its efficacy.	Comments noted.
TUC	General	You will be aware that the Scottish Medicines Consortium and the London Cancer New Drugs Group have already approved the use of Alimta and that local centres in Scotland, Manchester Liverpool, London and Newcastle are already offering Alimta to mesothelioma patients.	The Committee recognised that pemetrexed may be widely used in some parts of the UK, but still feels that its recommendation is appropriate on the basis of the currently available evidence..
TUC	Recommendations	If the preliminary guidance becomes final it will mean that the only treatment available for mesothelioma will be those that have not been properly assessed or are currently unlicensed for specific use against this disease.	Comments noted.
TUC	Recommendations	We hope that NICE will support the use of Alimta for the treatment of mesothelioma as there appears little doubt that it has been successful in increasing the life expectancy, and quality of life, of those patients who have been treated to date. We do not believe that the average cost of £8,000 for a full course is unreasonable and it is estimated that the budget impact of Alimta on the NHS would be less than £3 million in the current year and around £5 million by the end of the decade. This is a small cost to pay for a treatment which can make so much difference.	Comments noted. The Committee does not consider the affordability of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).