Pemetrexed disodium for the treatment of malignant pleural mesothelioma:

a systematic review & economic evaluation

Addendum

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1 Introduction

Currently in the UK there is no accepted standard treatment regimen for the malignant pleural mesothelioma (MPM). The most commonly used treatment regimens include MVP (mitomycin V, vinblastine and cisplatin) combination, single agent vinorelbine and supportive care. None of these agents however are licensed for the treatment of MPM.

This addendum presents additional material relating to questions regarding comparability between the innovative therapy (pemetrexed combined with cisplatin for the treatment of malignant mesothelioma) and other treatments, and the relevance of the choice of comparator to the assessment of effectiveness and cost-effectiveness in the treatment of MPM.

The issues addressed below are as follows:

1. Is cisplatin monotherapy a suitable comparator for pemetrexed + cisplatin in the UK context?
2. How well can effectiveness/survival be estimated for chemotherapy regimens commonly used in the UK to treat patients with MPM?
3. How well can effectiveness/survival be estimated for active supportive care alone as provided in the UK to treat patients with MPM?
4. What conclusions, if any, can be drawn on the cost-effectiveness of pemetrexed + cisplatin compared to other chemotherapy regimens and/or active supportive care?

Prior to directly dealing with these issues, it is appropriate to provide commentary on two important topics. Firstly, background information on survival estimation and trends relating to MPM, and secondly, a through provision of a more detailed description and critique of the industry submitted Model 2 than was included in the main report.

2 Survival in malignant mesothelioma

Five retrospective studies have been traced which describe survival experience in unselected patient series covering periods ranging between 1950 and 1985 (*Table* A.1). Overall median survival from diagnosis varies between 7 and 12 months, with the median time from symptoms to diagnosis ranging between about 3 and 6 months.

Table A.1 Early retrospective and registry studies of survival in malignant mesothelioma

Author (date)	Location	Indication	Patients	Period	Histology	Survival	Prognostic factors
Adams (1986) [1]	USA	Diffuse MM	92	1950 - 1980	Epithelial 42 Mixed 29 Sarcomatous 21	12 months 5 months 3 months (Median from diagnosis)	Sex, Epithelial
Chailleux (1988) [2]	France	Diffuse MM	167	1955 - 1985	Epithelial 131 Mixed 25 Sarcomatous 7	1 year survival: 39% from diagnosis 54% from symptoms	Age, Laterality, Any treatment
Tammilehto (1992) [3]	Finland	Histologically confirmed MPM	65	1960 - 1980	Not stated	12 months from diagnosis 18 months from symptoms (Median)	Stage, Performance status
Ruffie (1989) [4]	Canada	Diffuse MM	332	1965 - 1984	Not stated	3.5 months to diagnosis 9 months from diagnosis (Median)	Stage, Platelet count, Asbestos exposure
Spirtas (1988) [5]	USA (9 states)	Histologically confirmed MPM	1475	1973 - 1984	Only available for 20% of cases	7 months (median from diagnosis)	Age, Sex, Stage, Any treatment, Location

There is no consistency of prognostic factors identified, even among the larger studies. The clear heterogeneity among the studies ensures that no deductions can be drawn in relation to the impact of treatment on survival, or of any temporal trends.

However, the large American Surveillance Epidemiology and End Results (SEER) Program database[6] offers the opportunity to look in more detail at trends in survival, by contrasting experience over different time periods. Data in *Table* A.2 appear to demonstrate clear improvement over time among males, both those under and over 65 years at diagnosis. However, the position relating to females is less compelling, with a declining trend in older patients and ambiguity among those under 65. It is possible that the smaller number of females in the registries may be significant here. Even if we accept the improving trend among males over 20 years, there are several potential confounding factors which should prompt caution in interpreting these figures:

- secular case-mix changes could have a strong influence
- case-finding and reporting practices may have changed over time
- the long-term trajectory of incidence following asbestos exposure may be interacting with variations in the inherent aggressiveness of disease leading to temporal distortions in survival patterns
- changes in clinical practice and the availability of specific treatments may also be influential on survival

Table A.2 5-year survival rates for white SEER patients from time of diagnosis by age & sex [6]

Age	**<65**		**65+**		**All ages**	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
1975-1979	5.0%	27.2%	2.6%	12.5%	4.0%	21.9%
1985-1989	8.2%	21.2%	2.8%	7.3%	4.9%	14.0%
1995-2001	10.2%	35.2%	4.7%	4.7%	6.5%	17.7%

Table A.3 (also from the SEER database[6]) is interesting in demonstrating the heterogeneity of MPM patients, with a small number of very long-term survivors. This is consistent with the need to employ a survival model with variable hazard rate, such as the Weibull, rather than an exponential model (with constant hazard).

Table A.3 5-year conditional survival rates for white SEER patients by conditional survival period (SEER registries 1975-2001)[6]

Conditional survival period (years)	**Probability of surviving a further 5 years**
1	17.1%
3	44.7%
5	60.7%
10	89.1%

Summary: Consideration of the limited literature available from Europe and North America, does not offer a basis for estimating typical expected survival in MPM, nor for identifying an unambiguous set of prognostic indicators for better survival. Long-term time trends in survival may suggest some improvement in life expectancy at diagnosis, at least in men, but cannot rule out that this may be artefactual due to several confounding effects. However, the data do strongly suggest that despite the generally poor prospect, a small number of patients may survive for several years.

3 Model 2: description and critique

The second spreadsheet model submitted by the manufacturer of pemetrexed is designed to estimate a set of economic comparisons between pemetrexed + cisplatin and various other chemotherapy regimens thought to be commonly used in the UK. The model is relatively simple in structure, relies on a variety of data sources to furnish parameter estimates, and is not designed to allow probabilistic sensitivity analysis.

The model considers only the fully supplemented population from the primary trial. The main components of the model are as follows:

Survival
For pemetrexed + cisplatin, the mean survival estimated in Model 1 was used. For other therapies (MVP, vinorelbine-based regimens and supportive care) evidence from various comparative and non-comparative studies was combined to obtain estimates of median survival, and these were then translated into an estimated mean survival using a multiplier derived from the primary trial.

Pemetrexed + Cisplatin Costs
The mean overall cost per patient estimated in Model 1 was used.

Drug Costs
Each comparator regimen was costed separately based on body surface area, standard dose levels (mg/kg), mean treatments per cycle, mean cycles per course, and list prices for the constituent drugs.

Administration Costs
These are based on the proportions of patients treated as in-patients or out-patients in the primary trial, multiplied by a corresponding NHS Reference Cost.

Serious Adverse Event / Treatment-Emergent Adverse Event Costs
Various comparative and non-comparative studies were combined with results of a clinician survey to derive estimated frequencies of each type of event associated with particular regimens. These were then multiplied by NHS Reference Costs for corresponding in-patient episodes.

Table A.4 Issues identified concerning the validity and reliability of Model 2

Model component	Issue	LRiG assessment	Impact on results
Survival	1. Single arms of non-comparative trials were combined without correction for case-mix differences, when estimating comparator survival	1. Results obtained cannot be considered meaningful, since variations between populations may serious alter estimates	1. Estimates obtained by this method cannot be meaningfully compared to survival in the P+C arm of the primary trial
	2 Median values from separate trial arms were combined by calculating a weighted average median	2. This is methodologically unsound and can result in introducing potentially large and unpredictable errors	2. Estimates obtained by this procedure are fundamentally unreliable
	3. Estimated median survival for comparators is converted to estimated means by a ratio (1.24) obtained from the P+C arm of the primary trial	3. This ratio varies for each treatment and the completeness of follow-up. LRiG survival model implies ratios of 1.189 for P+C and 1.156 for C	3. P+C survival estimates are not affected, but comparators may have survival overstated by 0.6-0.8 months. This would lead to slightly more favourable ICERs for P+C
	4. Mean survival in the P+C arm is only estimated to 29 months (duration of trial data). Comparators are implicitly subject to the same limit by use of mean:median ratio derived from P+C arm	4. LRiG survival estimates to end of life give slightly greater survival benefit	4. Slightly conservative assumption for P+C
Pemetrexed +Cisplatin Costs	Adverse-event costs in the primary trial were restricted to those which incurred an in-patient episode. No attempt was made to distinguish treatment-related AEs from other serious events, nor to consider costs arising from other AEs requiring ambulatory treatment	It is difficult to be sure that Adverse Event costs obtained from the trial (as used in the P+C arm of Model 2) are directly comparable to Adverse event / treatment-emergent costs for comparators estimated in Model 2	The potential size of any discrepancy in incremental costs is likely to be small, and is unlikely to impact significantly on estimated ICERs
Drug Costs	Sources for the mean number of cycles of therapy given for each of the comparators are limited and confusing MVP: both the quoted studies report only a median number of cycles given (3), but not the mean, though this can be deduced to be 4 and <3.5 respectively Vinorelbine: two small studies were used (monotherapy n= 29, Vin+oxalyplatin n = 26) reporting only median cycles given as 2 and 4 respectively	This is important in driving both the acquisition and administration costs of each comparator. The higher mean cycle values in the model (4.7 MVP, 6.125 Vinorelbine, 4.0 Vin +/- platinum) are derived from the market research exercise. It is not clear whether these refer to maximum intended cycles of treatment or the actual mean cycles given (after withdrawals for any reason)	If mean cycles are smaller than those “reported” it could have a large impact on ICERs, particularly for Vinorelbine-based regimens

Model component	Issue	LRiG assessment	Impact on results
Administration Costs	1. See Drug Costs issue above	1. See Drug Costs issue above	1. See Drug Costs issue above
	2. In all the main analyses, it is assumed that 63% of patients required hospitalisation for treatment, in line with the primary trial	2. This is an unreasonable assumption for Vinorelbine-based therapies, since both the cited trials report 100% out-patient administration. The MVP references do not provide information on in or out-patient status	2. Requiring in-patient administration greatly increases the cost in the comparator arm for Vinorelbine-based therapies, and may also do so for MVP. A sensitivity analysis is included assuming 100% outpatient administration, but this should be consider the base case
Serious Adverse Event / Treatment-Emergent Adverse Event Costs	1. AE event frequencies for P+C are obtained from the primary trial and in restricted to events leading to hospitalisation. For comparators UK oncologist survey results are combined with source papers to obtain estimated figures	1. It is not clear that reported frequencies in source papers, oncologist survey and the primary trial are compatible, either in magnitude (survey figures often much higher and usually in 'round figures') or in being limited only to hospitalisations	1. Use of the survey data increases the frequencies and thus the associated costs for the comparators and may bias the results in favour of P+C
	2. In both the primary trial and in estimation for comparators, it is not clear how hospitalisations are counted	2. Frequently more than one serious AE may be reported in relation to the same incident, leading to the likelihood of significant 'double-counting'	2. AE hospitalisation costs generally may be overstated in either or both arms of the analysis
	3. For P+C, AEs which are not associated with hospitalisation are not costed. For comparators all AEs are assumed to require hospitalisation	3. There is significant scope for under-costing the P+C arm, and over-costing comparators	3. Important unquantifiable potential for bias
Concomitant medications	Costs for concomitant medications are included in the P+C costs, but are excluded from the comparator costs due to lack of evidence	Costs are almost certainly under-estimated for P+C, since the calculation appears not to take into account the duration of use, which in a number of case may extend beyond the initial prescription	Unclear whether the combined effect of undercosting P+C, and omission of costs for comparators will bias results in either direction. However, the overall effect is likely to be small

Summary: A number of issues and concerns with Model 2 have been identified by the Assessment Team and are detailed in *Table* A.4. The most serious of these relate to the sources used and methods of calculation employed in obtaining estimates of mean survival for the various comparators. Since these values are fundamental to the remainder of the model, the lack of methodological validity and the consequent inherent unreliability of derived economic results led the Assessment Team to conclude that Model 2 results could not be considered a useful basis for decision-making.

4 Cisplatin as comparator for malignant mesothelioma

4.1 Cisplatin monotherapy

A total of five published studies report information concerning treatment of malignant mesothelioma with cisplatin monotherapy; these are detailed in *Table* A.5. All but one are non-comparative phase I or phase II studies with very limited patient numbers and response rates varying between 12.5% and 35.7%.

4.2 Cisplatin combination therapies

A further 26 non-comparative studies were found involving 18 different regimens (*Table* A.6), involving between 11 and 69 patients, and reporting response rates in the range of 6-48% and median survival in the range of 6-15 months. The majority of these papers together with other non-cisplatin studies were the subject of a systematic review of phase II trials published in 2002 by Bergmans *et* al.[7] They grouped response rates into four classes based on the presence or absence of cisplatin and doxorubicin in the regimen and obtained results from meta-analysis shown in *Table* A.7 (reproduced from their *Table* 5):

Table A.5 Published studies including cisplatin monotherapy

Study name	Interventions	Study design, n	No of patients	Tumour type	Overall median survival	Response rate
Van MEERBEECK [8] 2005	Arm A: Cisplatin Arm B: Cisplatin plus raltitrexed	**Phase III, RCT**	250 (213 with measurable disease)	Malignant pleural mesothelioma	Cisplatin: 8.8 mo Raltitrexed:11.4 mo	Cisplatin: 13.6% Raltitrexed: 23.6%
PLANTING [9] 1994	High dose cisplatin	Phase II, non comparative	14	Malignant pleural mesothelioma, stage II	NR	PR: 36% (ITT)
REBATTU [10] 1993	High dose cisplatin (200 mg/m^2)	Phase II, non comparative	13 (10 pleural, 3 peritoneal)	Malignant mesothelioma	11 mo	PR: 23% (ITT)
ZIDAR[11] 1988 (SWOG Study)	Cisplatin	Phase II, non-comparative	35 (pleural 32, peritoneal 2, prior CT or RT allowed)	Malignant mesothelioma	7.5 mo (all pts) 9 mo (responders)	PR: 14.3%
MINTZER [12] 1985	Cisplatin	Phase II, non-comparative	25 (24 pts evaluated, 7 pts received prior CT)	Malignant mesothelioma	5 mo	PR: 12.5%

Table A.6 Published studies of cisplatin-containing combinations [13, 14]

Study name	Interventions	No of patients	Response Rate (%)	Median survival (mo)
Chahinian 1993	Cisplatin + doxorubicin	35	14	8.8
Ardizzoni 1991	Cisplatin + doxorubicin	24	25	10
Henss 1988	Cisplatin + doxorubicin	19	46	12.3
Parra 2001	Cisplatin + doxorubicin + IFN-α	35	29	9.3
Shin 1995	Cisplatin + doxorubicin cyclophosphamide	23	26	14
Pennucci 1997	Cisplatin + doxorubicin + mitomycin	23	21	11
Breau 1991	Cisplatin + doxorubicin + mitomycin+ bleomycin	25	44	NA
Samuels 1998	Cisplatin + dihydro-5-azacytidine (DHAC)	29	17	6.4
Planting 1995	Cisplatin + etoposide	25	24	NR
Eisenhauer 1988	Cisplatin + etoposide	29	12	NA
Byrne 1999	Cisplatin + gemcitabine	21	47.6	10.3
Van Haarst 2000	Cisplatin + gemcitabine	22	15	10
Nowak 2002	Cisplatin + gemcitabine	53	33	11.2
Castagneto 2005	Cisplatin + gemcitabine	35	26	13
Soulie 1996	Cisplatin +IFN-α	26	40	12
Pass 1995	Cisplatin + IFN-α + tamoxifen	36	19	8.7
Trandafir 1997	Cisplatin +IFN-α	30	27	15
Nakano 1999	Cisplatin + irinotecan	15	26.7	7.1
Chahinian 1993	Cisplatin + mitomycin	35	26	7.7
Tansan 1994	Cisplatin + mitomycin + IFN-α	20	11	15
Middleton 1998	Cisplatin + mitomycin + vinblastin (MVP)	39	20	6
Metintas 1999	Cisplatin + mitomycin + IFN-α	43	23	11.5
Thodtman 1999	Cisplatin + pemetrexed (Phase I)	11	45	NA
Kaukel 1990	Cisplatin + pirarubicin	39	15	10.5
Fizazi 2000	Cisplatin + paclitaxel	18	6	12
Berghmans 2005	Cisplatin + epirubicin	69	19	13.3

Table A.7 Response rates according to treatment groups[7]

Therapy group	Number of responders	Number exposed	Response rate (%)	95% CI
Cisplatin, no doxorubicin	127	547	23.2	19.7-26.8
Doxorubicin, no cisplatin	24	213	11.3	7.0-15.5
Cisplatin + doxorubicin	43	151	28.5	21.3-35.7
Neither	164	1409	11.6	10.0-13.3

The manufacturer's submission provides evidence from market research of current usage of first-line therapies in the UK. This suggests that although use of cisplatin is very low, there is no evidence of any use of doxorubicin with this group of patients.

Summary: There is limited evidence of efficacy for any cisplatin chemotherapy regimen for MPM. However, there is meta-analytic evidence suggesting that cisplatin is probably at least as active as other compounds, as monotherapy and in combination. Since doxorubicin is not currently used at all in the UK and is more expensive than cisplatin, it is reasonable to consider cisplatin monotherapy as a reasonable comparator for pemetrexed + cisplatin, as compared in the primary trial.

5 Other comparators: chemotherapy and active supportive care

The manufacturer's submission identified a total of eight published studies as sources for information relating to potential UK comparator regimens for pemetrexed + cisplatin other than that used in the primary trial (cisplatin monotherapy). These are detailed in *Table* A.8, and include four relating to chemotherapy and four to supportive care.

Table A.8 Published studies of current treatment options in the UK

Study name	Data collection	Interventions	Study design, n	No of patients	Tumour type	Overall median survival	Response rate
MIDDLETON [15] 1998	October 1986-June 1997	MVP	Non-comparative , prospective study	39	Malignant mesothelioma *(unclear whether pleural or peritoneal)*	6 mo (reange:1-16 mo)	PR: 20% No complete response
ANDREOPOULOU [16] 2004	October 1986-May 2002	MVP	Non-comparative , prospective study	150	Pleural mesothelioma	7 mo	15.3%
STEELE [17] 2000	April 1998-January 1999	Vinorelbine	Phase II, non-comparative open-label study	29	Malignant pleural mesothelioma	10.6 mo	PR: 24%
FENNELL[18] 2005	November 2000 (cut-off date)	Vinorelbine and oxaliplatin	Phase II, non-comparative study	26	Malignant pleural mesothelioma	8.8 mo	PR: 23%
AZIZ[19] 2002	1989-1998	Best supportive care	Retrospective study	191	Malignant pleural mesothelioma	7 mo (range: 1-19 mo)	Not reported
CALAVREZOS [20] 1988	March 1981-February 1985	Group A: Combined chemotherapy (doxorubicin, vindesine, cyclophosphamide) Group B:Supportive care Group C: Pts not eligible for treatment (also received supportive care)	Prospective comparative study	Group B: 36 Group C: 39 (5 pts received chemotherapy)	Malignant pleural mesothelioma	Group B: 7 mo Group C: 5 mo	Not reported
CHAN[21] 2003	Review of medical records, between 1996-2001, Singapore General Hospital,	Supportive care (12 pts), chemotherapy (4 pts)	Retrospective chart review	16	Pleural mesothelioma (13 pts), Peritoneal mesothelioma (3 pts)	7 mo	Not reported
JUBELIRER [22] 1997	Review of medical records between 1966-1992	Supportive care only (26 pts) Combination of 3 treatment modalities (24 pts)	Retrospective chart review	50	Malignant pleural mesothelioma	4 mo	Not reported

5.1 MVP survival

The manufacturers have employed a median survival of 6.79 months as a weighted average of reported medians in the two studies (see *Table* A.4 for methodological problems with this), and derived from this an estimated mean survival of 8.4 months. However, Andreopoulou[16] shows that median survival is strongly influenced by performance status with 10 months for PS0/1 and only 6 months for PS 2/3. Using the PS case-mix in the primary trial, we may infer that a more reasonable median survival to use in Model 2 would be about 9.5 months. This would lead to an estimated mean survival of 11.8 months in Model 2, about 40% greater than that shown as the base case. This alteration alone changes the submitted incremental cost per QALY gained from £21,731 to £47,972.

5.2 Vinorelbine survival

The two studies cited in the manufacturer's submission are both small (29 and 26 patients only) and therefore subject to a large degree of uncertainty in terms of survival estimates. Steele[17] reports a median survival of 10.6 months for monotherapy, whereas Fennel[18] appears to report a median of 8.8 months for vinorelbine+oxaliplatin. However, this is probably a misreading of the Fennel paper: examination of the published survival curves yields a median survival of 8.45 months and a mean of 8.9 months (AUC estimate). For Model 2, a strong assumption has been made that all vinorelbine regimens are of equal efficacy (i.e. that addition of other active treatments yields no additional benefit), which must be open to question. Only very small alterations in vinorelbine survival (about 1%) are necessary in Model 2 to increase the incremental cost per QALY gained from the submitted base value to more than £30,000.

5.3 Active/Best Supportive Care

There is an essential difference between the majority of patients currently receiving supportive care, for whom any chemotherapy may not be suitable due to their performance status and life expectancy, and the much smaller numbers who might be suitable for chemotherapy. Not surprisingly it would be difficult to mount a large-scale randomized trial of such patients on both ethical and human grounds. It is therefore not surprising that the evidence base for survival in patients receiving only

supportive care is particularly weak and of questionable relevance to the cost-effectiveness of pemetrexed+cisplatin.

Three of the four studies cited in the manufacturer's submission are non-comparative retrospective case reviews none of which can be considered to be drawn from equivalent patient populations. The single comparative trial[20] (n=36) involves patients clearly with much poorer prospects than those in the primary trial. By combining these studies the industry submission offers a median survival of 6.7 months, and an estimated mean of 8.3 months.

An alternative approach may be offered by a meta-analysis undertaken by Curran, [23] designed to consider prognostic factors for survival in MPM. This involved analysis of patient data from five phase II trials which failed to show efficacy for candidate compounds. The advantage of this patient group is that they are more likely to represent patients who might normally be considered appropriate for chemotherapy. If this is accepted, then the failure of efficacy suggests that their combined survival experience may be a reasonable proxy for supportive care without active chemotherapy. This study reported an overall median survival of 8.4 months, with a strong trend by performance status (10.7 months for PS 0, and 7.2 months for PS 1 or 2). Substituting this value into Model 2 increases the incremental cost per QALY gained from £32,066 to £48,779, indicating that the cost-effectiveness of pemetrexed+ cisplatin relative to supportive care may be subject to very substantial uncertainty.

***Summary**:* The evidence base for estimating survival in other comparators (including supportive care) is too weak to be taken seriously as a basis for decision making. The use to which these results have been put is in some instances misleading or at least open to question, and relatively small variations in estimated survival are likely to lead to substantially increased cost-effectiveness ratios, likely to yield values beyond the normal range of acceptability.

6 Conclusions

Returning to the original questions posed we make the following observations (*Table* A9):

Table A.9: Conclusions

Question	Response
1. Is cisplatin monotherapy a suitable comparator for pemetrexed + cisplatin in the UK context?	Cisplatin appears to be as active a compound as others in the literature, is used very occasionally in the UK, and because it has a low acquisition cost represents a meaningful test of cost-effectiveness for pemetrexed + cisplatin.
2. How well can effectiveness/survival be estimated for chemotherapy regimens commonly used in the UK to treat patients with malignant mesothelioma?	The evidence base for survival for MVP and vinorelbine regimens is very weak, and not based on comparative trials. Great caution should be exercised in use of these results.
3. How well can effectiveness/survival be estimated for active supportive care alone as provided in the UK to treat patients with malignant mesothelioma?	The direct evidence base for survival with support care only is even weaker. Also there is a serious problem concerning the legitimacy of supportive care as a comparator for chemotherapy, since the great majority of patients currently receiving supportive care will not be suitable for chemotherapy. Indirect evidence may suggest that survival on supportive care may be rather better than it appears in the cited studies.
4. What conclusions, if any, can be drawn on the cost-effectiveness of pemetrexed + cisplatin compared to other chemotherapy regimens and/or active supportive care?	On the basis of the above, we continue to believe that the results presented from Model 2 should be considered unreliable and potentially misleading. If it accepted that cisplatin is a reasonable comparator for pemetrexed + cisplatin then this would appear to be the most appropriate basis for assessing cost-effectiveness.

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