NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Pemetrexed disodium for the treatment of malignant pleural mesothelioma

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Malignant mesothelioma is a type of cancer that occurs in the mesothelium, a membranous lining that surrounds most internal organs. The mesothelium surrounding the lungs is known as the pleura and the mesothelium in the abdominal cavity is called the peritoneum. Cancers occurring in these lining tissues are named pleural mesothelioma and peritoneal mesothelioma, respectively. Over 90% of mesothelioma with a known first site occurs as pleural mesothelioma.

Malignant pleural mesothelioma (MPM) is a rapidly progressive malignancy of insidious onset. Presentation and diagnosis often occur at an advanced stage and the prognosis for most patients is extremely poor. Median survival from diagnosis varies from study to study, with a range of 8–14 months. Age,

tumour histology, tumour stage at diagnosis and performance status have been shown to be independent prognostic factors.

Most patients present with chest pain and dyspnoea, with pleural effusions evident on examination. Fatigue, profuse sweating, weight loss, anorexia and difficulty in swallowing become common as the disease progresses.

Tumours may be epithelioid, sarcomatoid or mixed. Epithelioid tumours are more common than the other two subtypes and have a better, albeit still poor, prognosis.

Staging provides prognostic information and is important in determining treatment strategy. There is no universally accepted staging system; however, the traditional Butchart staging system is gradually being replaced with a tumour nodes metastases (TNM) system developed by the International Mesothelioma Interest Group. According to the British Thoracic Society (British Thoracic Society Standards of Care Committee 2001), the new system is thought to have better prognostic value; however, its use requires surgical intervention to achieve full staging. The stages are defined as follows.

- Stage 1: the tumour affects one layer of the pleura only. It may have grown into the pericardium and the diaphragm.
- Stage 2: the tumour has spread to both layers of the pleura on one side of the body only.
- Stage 3: the tumour has spread to the chest wall, oesophagus or lymph nodes on the same side of the chest.
- Stage 4: the tumour has spread via the bloodstream to other organs in the body such as the liver, brain or bone or to lymph nodes on the other side of the chest.

Over 99% of deaths caused by MPM have been linked to asbestos exposure. When asbestos fibres are inhaled or swallowed, they can cause scarring of the lung tissues, cancer of the bronchial tree (lung cancer) and sometimes cancers in the pleura and peritoneum. A wide range of occupations, notably shipbuilding, railway engineering and asbestos product manufacture, are associated with an increased risk of MPM. Those involved in building

demolition, maintenance and repair are particularly at risk. Family members of people whose work clothes were contaminated have also developed MPM. The condition is significantly more common in men, with a male:female ratio of 5:1. Age at presentation is usually between 60 and 79 years.

MPM does not usually develop until 10–60 years after exposure to asbestos, the median time being about 40 years. Data from 2003 suggest that currently about 1850 people in the UK are diagnosed with MPM each year. It is estimated that the number of people diagnosed with MPM in the UK will increase to a peak of over 2000 cases each year between 2011 and 2015, reflecting a lag from the highest use of asbestos in the 1970s. An estimated 65,000 cases are expected to occur between 2002 and 2050. The use of asbestos was banned in the UK in 1999.

1.2 Current management

There is no standard treatment pathway for MPM in the UK. The clinical management of MPM is multimodal and a patient may receive a combination of treatments.

Surgical resection in the form of extrapleural pneumonectomy is an option for the small proportion of patients (1–5%) whose tumours are at stage 1 or 2. There have been no randomised controlled trials (RCTs) to establish the effectiveness of surgery and its role is controversial. In observational studies, 5-year survival rates as high as 15% have been reported; however, operative mortality appears to be high outside specialist centres.

For the overwhelming majority of patients, for whom surgery is not indicated, the aim of treatment is to improve symptoms, prolong life and slow progression of the disease. For approximately 50% of patients, treatment is limited to active symptom control (ASC) or best supportive care (BSC). Although there is no standard definition of these terms, they appear to be used more or less interchangeably to refer to treatments intended to maximise quality of life, without a specific anticancer regimen. For MPM patients, this might include interventions to manage pain and dyspnoea and to address psychosocial problems. Treatments may include draining the pleural cavity of

excess fluid and applying a talc pleurodesis (the insertion of talc to prevent further fluid accumulation), palliative radiotherapy, analgesics, steroids, appetite stimulants and bronchodilators.

Radical radiotherapy is not widely used in MPM because it does not appear to significantly affect survival, and the large volumes required for pleural coverage result in high toxicity. However, radiotherapy is used as prophylaxis following invasive procedures and as a palliative treatment for pain or chest wall masses.

There is no standard chemotherapy treatment for MPM. Pemetrexed in combination with cisplatin is the only chemotherapy regimen that is currently licensed for this indication, although in practice, a wide variety of single-agent and combination regimens are used. Alkylating agents, anthracyclines, platinum compounds, antifolates and mitomycin C have demonstrated response rates of 0–45% in clinical trials. Single-agent vinorelbine and the MVP (mitomycin C, vinblastine and cisplatin) combination are among the treatments most commonly used in the UK and have been shown to give good symptom relief with acceptable toxicity. To date there have been no RCTs comparing survival and symptom control in patients receiving chemotherapy with those receiving ASC/BSC. It is therefore uncertain if chemotherapy offers any benefit over ASC/BSC in terms of survival and quality of life. Currently, chemotherapy is often given as part of a clinical trial.

MPM is not mentioned in the NHS Cancer Plan and there is currently no NICE guidance relating to the treatment of MPM. The British Thoracic Society provides advice on the management of MPM in its ‘Statement on malignant mesothelioma in the United Kingdom’, but does not refer to this document a guideline because it ‘is not strictly evidence based… and, in many aspects of the subject, there are insufficient randomised trials upon which to base guidelines.’ (British Thoracic Society Standards of Care Committee 2001).

2 The technology

Table 1 Summary description of technology

Generic name	Pemetrexed disodium
Proprietary name	Alimta
Manufacturer	Eli Lilly
Dose	500mg/m^2 every 3 weeks
Acquisition cost excluding VAT (*BNF* edition 50)	£800/500-mg vial

Pemetrexed disodium is indicated, in combination with cisplatin, for the treatment of chemotherapy-naive patients with unresectable malignant pleural mesothelioma.

It is a multi-targeted anticancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. It acts by inhibiting thymidylate synthetase and dihydrofolate production, and hence suppressing the synthesis of purines and pyrimidines.

Cisplatin is a platinum-based chemotherapeutic agent that has antitumour activity, either as a single agent or in combination, for a number of different cancers. It is available in the UK from Bristol-Myers Squibb, Mayne Pharma, Pfizer and Wockhardt.

Pemetrexed disodium is administered as a 10-minute intravenous infusion on the first day of each 21-day cycle. It is followed approximately 30 minutes later by cisplatin (recommended dose 75 mg/m^2) infused over 2 hours.

In order to reduce toxicity, patients treated with pemetrexed must receive folic acid and vitamin B_{12} supplementation. To reduce the incidence and severity of skin reactions, premedication with a corticosteroid is recommended.

Adverse effects commonly associated with pemetrexed include nausea, vomiting, fatigue and leukopenia, particularly in the neutrophil component. Skin rash, mucositis and liver function abnormalities have also been reported.

Cisplatin causes nausea and vomiting in the majority of patients. This is controllable in 50%–80% of cases by $5HT_3$ antagonists. Serious toxic effects

effects on the kidneys, bone marrow and ears are common, and serum electrolyte disturbances, hyperuricaemia, allergic reactions and cardiac abnormalities have also been reported.

3 The evidence

3.1 Clinical effectiveness

The systematic review undertaken by the Assessment Group identified a single RCT of pemetrexed. The 'Evaluation of mesothelioma in a phase III trial with alimta and cisplatin' (EMPHACIS) study compared pemetrexed plus cisplatin with cisplatin alone. This was a single-blind, international multicentre trial in 448 patients (see Table 2 on page 7)

The literature search carried out by the Assessment Group did not identify any studies that compared the effectiveness of pemetrexed with chemotherapy regimens more commonly used in the UK, such as MVP and vinorelbine. Similarly, there were no studies comparing pemetrexed with ASC/BSC.

In the absence of direct comparisons, Eli Lilly's submission presents data on median survival and response rates for alternative treatments commonly used in UK clinical practice (MVP, vinorelbine, vinorelbine plus oxaliplatin, and ASC/BSC). These were obtained by updating a published systematic review of chemotherapy in MPM and from a systematic search for studies of ASC/BSC in MPM. The data presented are mostly from small (n < 40), non-comparative observational or phase II studies. As such, the validity of any comparison of these efficacy data with the results of the EMPHACIS RCT is uncertain.

3.1.1 The EMPHACIS trial

The characteristics of the EMPHACIS trial are summarised in Table 2.

Table 2 EMPHACIS trial characteristics

Study name	Intervention	Control	Outcomes	Inclusion criteria	Exclusion criteria	Median follow-up
EMPHACIS 2003	Pemetrexed 500 mg/m^2 over 10 minutes followed 30 minutes later by cisplatin 75 mg/m^2 over 2 hours n = 226	Normal saline over 10 minutes followed 30 minutes later by cisplatin 75 mg/m^2 over 2 hours n = 222	**Primary outcome** • Survival **Secondary outcomes** • Time to progressive disease • Time to treatment failure • Tumour response rate • Duration of response • Pulmonary function • Symptomatic benefit (using Lung Cancer Symptom Scale)	• Age ≥ 18 years • Life expectancy ≥ 12 weeks • Uni- or bi-dimensionally measurable disease • Karnofsky performance status ≥ 70	• Prior chemotherapy • Second primary malignancy • Brain metastases • Patients unable to interrupt NSAIDs	10 months

NSAID, non-steroidal anti-inflammatory drug; RCT = randomised controlled trial.

In both arms, treatment was administered on the first day of each 21-day cycle. The median number of cycles given was 6 (range 1–12) in the pemetrexed plus cisplatin arm and 4 (range 1–9) in the cisplatin arm.

During the early stages of the trial, severe toxicity (including drug-related death, neutropenia, febrile neutropenia and diarrhoea) occurred in the pemetrexed arm. This led to a decision to add dietary folic acid and vitamin B_{12} supplementation to the trial protocol (in both treatment arms, to preserve blinding). With effect from the date of the protocol change, all patients in both arms received supplementation, resulting in three patient subgroups defined by supplementation status: never supplemented (n = 70), partially supplemented (n = 47) and fully supplemented (n = 331). The primary analysis was performed on all patients who were randomised and treated (intention to treat [ITT] population). A subgroup analysis was performed on fully supplemented patients. A further (apparently post-hoc) subgroup analysis was performed on patients with advanced disease (stage 3/4) as it was felt that most patients (> 80%) presenting to clinicians would fall into this category.

3.1.2 Efficacy results

A summary of the main results of the trial is given in Table 3.

Table 3 Summary of main results from the EMPHACIS trial

	ITT		FS		FS Advanced Disease	
Outcomes	Pemetrexed + cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed + cisplatin (n = 168)	Cisplatin (n = 163)	Pemetrexed + cisplatin (n = 125)	Cisplatin (n = 122)
Survival (months)						
Median	12.1	9.3	13.3	10	13.2	8.4
95% CI	10.0–14.4	7.8–10.7	11.4–14.9	8.4–11.9	9.3–14.9	6.8–10.2
HR	0.77		0.75		0.63	
Log-rank p value	0.02		0.051*		0.003	
% censored	35.8	28.4	43.5	36.8	40.8	27.0
1-year survival (%)	50.3	38	56.5	41.9	Not reported	Not reported
p value	0.012		0.011		Not Reported	
Time to progressive disease (months)						
Median	5.7	3.9	6.1	3.9	5.6	3.0
95% CI	4.9–6.5	2.8–4.4	5.3–7.0	2.8–4.5	4.7–7.3	2.7–4.3
HR	0.68		0.64		0.54	
Log-rank p value	0.001		0.008		<0.001	
Tumour response rate (%)	41.3	16.7	45.5	19.6	43.5	16.4
95% CI	34.8–48.1	12.0–22.2	37.8–53.4	13.8–26.6	34.7–52.7	10.3–24.2
Fisher's p value	< 0.001		< 0.001		< 0.001	

CI, confidence interval; FS, fully supplemented; HR, hazard ratio; ITT, intention to treat.
* A p value of 0.039 was obtained using the Wilcoxon method.

3.1.3 Quality of life

Quality of life was evaluated using the Lung Cancer Symptom Scale–Meso instrument. Several aspects of quality of life were evaluated, including pain, dyspnoea, fatigue, anorexia and cough. At 18 weeks, patients treated with pemetrexed plus cisplatin demonstrated statistically significant symptomatic improvements when compared with those who received cisplatin alone. This was the case in both the ITT and fully supplemented populations.

3.1.4 Adverse events

Grade 3/4 adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone. The most commonly reported grade 3/4 toxicities in pemetrexed plus cisplatin patients were: neutropenia (27.9%), leukopenia (17.7%), nausea (14.6%) and vomiting (13.3%). Supplementation with folic acid and vitamin B_{12}

resulted in a consistent reduction in the severity and incidence of toxicity (except for dehydration) in the pemetrexed plus cisplatin arm. The most common severe adverse events in fully supplemented patients were: neutropenia (23.2%), leukopenia (14.9%), nausea (11.9%) and vomiting (10.7%).

3.1.5 Limitations of the EMPHACIS trial

The trial comparator, cisplatin, does not reflect standard treatment in the UK and this point has been noted by several consultees. However, in the most recent systematic review of chemotherapy in MPM, the Lung Cancer Disease Site Group of Cancer Care Ontario concluded that, as cisplatin is unlikely to reduce survival in MPM patients, the EMPHACIS trial provides sufficient indirect evidence that pemetrexed plus cisplatin combination chemotherapy improves survival and quality of life for patients.

Cisplatin was selected as the comparator for the EMPHACIS study for the following reasons.

- There is no established standard therapy for MPM.
- At the time of the trial, no chemotherapy drugs were licensed for the treatment of MPM.
- No combination chemotherapy regimen had shown an advantage over a single agent.
- The combination of pemetrexed plus cisplatin had been shown to have clinically meaningful antitumour activity in a phase I trial and single-agent cisplatin was deemed an acceptable comparator to attempt to delineate the effect of pemetrexed.

The Assessment Group suggests that the interpretation of the results of the EMPHACIS trial may require a degree of caution and notes that the trial was restricted to patients with a Karnofsky performance status of 70 or greater, (that is, those who were relatively fit). This may be inconsistent with the expected patient population.

In addition, accurate staging of mesothelioma is acknowledged to be difficult. It is therefore unclear whether trial participants were accurately and consistently staged across all centres and consequently and this may have implications for the external validity of data from the fully supplemented with advanced disease subgroup, which appears to show the greatest survival benefit.

3.1.6 Summary of clinical effectiveness section

Due to insufficient data, it was not possible to perform a meaningful comparison of the efficacy of pemetrexed with that of other treatments commonly used to treat MPM in clinical practice.

The results of the EMPHACIS trial suggest that pemetrexed plus cisplatin confers a survival benefit of approximately 3 months, compared with cisplatin alone. The combination treatment also appears to demonstrate advantages in terms of 1-year survival, disease progression, tumour response and quality of life. Pemetrexed plus cisplatin may offer a greater benefit (versus cisplatin) in patients with advanced (stage 3/4) disease.

Supplementation with folic acid and vitamin B_{12} is necessary in order to ensure an acceptable toxicity profile. However, pemetrexed plus cisplatin still causes serious adverse events in a significant proportion of fully supplemented patients.

The interpretation of the trial results is complicated by the choice of trial comparator and the characteristics of the trial population.

3.2 Cost effectiveness

Two cost-effectiveness models were submitted by Eli Lilly. The first of these, model 1, compares pemetrexed plus cisplatin with cisplatin alone. The second, model 2, compares pemetrexed plus cisplatin with MVP, vinorelbine with or without platinum, and ASC/BSC.

The literature search carried out by the Assessment Group identified a single cost-effectiveness study. This was in the form of a conference abstract/presentation, so little information was reported. The model underlying

the study was based on individual patient data (IPD) from the EMPHACIS trial and was a forerunner of the submitted model 1. A review of this study can be found in section 5.3 of the Assessment Report.

The Assessment Group used the manufacturer's model 1 as the basis for its own economic analysis.

3.2.1 Manufacturer's model 1

Model 1 is based on IPD from the EMPHACIS trial and compares pemetrexed plus cisplatin with cisplatin alone. The time horizon is 29 months, reflecting the trial follow-up period. The model considers four subgroups: fully supplemented patients; fully supplemented patients with advanced disease; fully supplemented patients with good performance status; and fully supplemented patients with advanced disease and good performance status. These subgroups were selected because they best reflected clinical practice (that is, patient characteristics at presentation and patients most likely to receive chemotherapy). No analysis is performed on the ITT population.

The perspective was that of the health service and only direct healthcare costs were included. Resource use was taken from the trial and unit costs from Department of Health reference costs or official drug price lists (BNF, MIMS). No discounting was applied to costs, as they were all incurred within 1 year.

Outcomes are expressed in terms of life years gained (LYGs) and quality adjusted life years (QALYs). Mean LYGs were estimated from the trial data using Kaplan-Meier curves. Outcomes were discounted at 3.5%, and varied between 0 and 6% in the sensitivity analysis.

Utility scores are taken from an ongoing observational study in non-small cell lung cancer patients who completed the EQ-5D health-related quality of life questionnaire just prior to chemotherapy. They are similar for both arms: 0.68 for the pemetrexed plus cisplatin arm and 0.69 for the cisplatin arm. The utility values are constant across age, disease status, treatment status and time.

A range of one-way and two-way sensitivity analyses were performed.

The incremental cost-effectiveness ratio (ICER) was £68,598 per QALY in the fully supplemented population. The ICER was more favourable in fully supplemented patients with advanced disease (£53,314), fully supplemented patients with good performance status (£48,099), and fully supplemented patients with advanced disease and good performance status (£47,567).

The results of the one-way sensitivity analysis on the fully supplemented population ranged from £41,681 to £202,719 per QALY. Results from the two-way sensitivity analysis ranged from £33,691 to £237,931 per QALY, the most favourable result being obtained by assuming a 20% reduction in drug costs alongside a 1.5-month increase in incremental survival.

3.2.2 Manufacturer's model 2

Model 2 indirectly compared pemetrexed plus cisplatin with MVP, vinorelbine (± platinum) and ASC. The time horizon was 29 months, reflecting the trial follow-up period. The perspective taken was that of the health service.

Costs and outcomes for pemetrexed plus cisplatin were taken from the fully supplemented population in model 1.

For the comparators, resource use data was gathered from market research surveys of oncologists, commissioned by the manufacturer. Unit costs were taken from Department of Health reference costs or list prices (BNF and MIMS). For drug costs, recommended average doses were assumed. Zero cost was assumed for ASC, as it was assumed that participants in trials of chemotherapy would have received similar levels of ASC to those provided to patients receiving ASC alone. Costs were not discounted as they were assumed to be incurred within 1 year.

Outcomes were expressed in terms of LYGs and QALYs. Median survival estimates were obtained from the literature reviews described in section 3.1. Exponential distributions were used to derive mean values for use in the cost-effectiveness analysis. The same utility values were used as in model 1, with the utility for cisplatin (0.69) being applied to all comparators in model 2.

A range of one-way and two-way sensitivity analyses were performed.

The incremental cost per QALY for pemetrexed plus cisplatin was £21,731 versus MVP, £28,391 versus vinorelbine ± platinum and £32,066 versus ASC.

The Assessment Group considered the evidence base underpinning model 2 to be weak. A comprehensive critique of model 2 will be provided by the Assessment Group prior to the committee meeting on 7 March 2006.

3.2.3 Assessment Group's economic analysis

The Assessment Group carried out its own economic analysis by inputting mean costs and outcomes into a simple formula (ICER = mean incremental cost / mean incremental effectiveness). The four subgroups considered in the original model 1 were analysed.

Mean costs were derived from the individual patient data in model 1. Costs were not discounted.

To derive mean effectiveness estimates, Weibull distributions were fitted to the Kaplan-Meier survival curves from the EMPHACIS trial, in order to model the survival distribution of patients who were still alive at the end of the follow-up period. Mean survival was estimated using the weighted least squares method and a discount rate of 3.5% was applied.

In both arms, the Assessment Group used mean utility values of 0.51–0.54 for each subgroup. These values were calculated based on an initial utility of 0.65, falling to 0.40 during a 100-day terminal period.

A probabilistic sensitivity analysis was carried out.

The Assessment Group's analysis resulted in an ICER of £60,561 per QALY in the fully supplemented population. The results were more favourable in fully supplemented patients with advanced disease (£49,051), fully supplemented patients with good performance status (£50,357) and fully supplemented patients with advanced disease and good performance status (£37,664).

The probability that pemetrexed plus cisplatin is cost effective at a willingness to pay threshold of £30,000 per QALY was less than 20% for all subgroups.

The ICERs generated by the Assessment Group are more favourable than those of the manufacturer. This is almost entirely due to the extrapolation of survival beyond the trial period in the Assessment Group's analysis.

3.2.4 Summary of cost-effectiveness section

All of the economic analyses are based on data from the EMPHACIS trial and are therefore subject to the limitations of this trial, as highlighted in section 3.1.5.

The economic analyses carried out by the manufacturer and the Assessment Group both indicate a cost per QALY of greater than £60,000 when pemetrexed plus cisplatin is compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin appears to be more cost effective in patients with advanced disease and/or good performance status but the cost per QALY versus cisplatin remains greater than £30,000 in all subgroups.

An indirect comparison submitted by the manufacturer indicates more favourable cost effectiveness of pemetrexed plus cisplatin versus MVP, vinorelbine and ASC but the model underlying these results relies on some very uncertain assumptions.

4 Issues for consideration

- Is cisplatin an appropriate comparator in terms of clinical and cost effectiveness? Can a recommendation be made based on a comparison with cisplatin?
- Are the results of the EMPHACIS trial robust, given the limitations highlighted in section 3.1.5?
- Are these results generalisable to the expected patient population, for example in terms of age and performance status?
- Is the effect of randomisation preserved in the fully supplemented subgroup? Should the economic analysis be based on results from an ITT analysis?

- Are the advanced disease and good performance status subgroups likely to be biased, especially given the subjective nature of these categorisations?
- How do patients value relatively small gains in survival versus the toxicity of chemotherapy?
- Is the manufacturer's model 2 valid? Why is pemetrexed plus cisplatin less cost effective when compared with cisplatin (model 1 and Assessment Group's analysis) than when compared with MVP, vinorelbine or ASC (model 2)?
- Is there a case for cost effectiveness to be considered in terms of LYGs instead of QALYs, given that survival may be considered to be the most relevant outcome for mesothelioma patients?
- Should special consideration be given to disease caused by occupational exposure?
- Could a positive recommendation for pemetrexed jeopardise recruitment into ongoing clinical trials for other mesothelioma treatments?
- Should an early review date be set in view of anticipated reporting of the MS01 trial (see section 5) in 2007?

5 Ongoing research

The Assessment Group and several consultees identified an ongoing phase III trial of MVP plus ASC or vinorelbine plus ASC versus ASC alone. The UK-based MS01 study, sponsored by the British Thoracic Society and the Medical Research Council, is expected to achieve its target recruitment during 2006 and results are likely to be reported in 2007. This study should help to address the gap in the current evidence base in relation to whether chemotherapy has any benefit over BSC.

No other ongoing studies were identified.

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Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Report: Dundar Y, Bagust A, Dickson R et al. (Liverpool Reviews and Implementation Group). *Pemetrexed disodium for the treatment of malignant pleural mesothelioma*, December 2005.

Corrections to the Assessment Report, January 2006

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Eli Lilly and Company Limited

II Professional/specialist and patient/carer groups:

- Asbestos Awareness Wales
- British Mesothelioma Interest Group
- Cancer BACUP
- June Hancock Mesothelioma Research Fund
- Royal College of Nursing
- Royal College of Physicians

III Commentator organisations (without the right of appeal):

- None

C Additional references used:

British Thoracic Society Standards of Care Committee (2001), Statement on malignant mesothelioma in the United Kingdom, *Thorax* 56:250–265.