Pemetrexed disodium for the treatment of malignant pleural mesothelioma

CONFIDENTIAL MATERIAL IS HIGHLIGHTED IN RED & UNDERLINED

Submission to:
National Institute for Health and Clinical Excellence

Submitted by:
Eli Lilly and Company Limited

1st AUGUST 2005

Correspondence to:

Dr Debbie Stephenson
Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hants
RG24 9NL

[redacted]

Answers That Matter.

The symptoms of malignant pleural mesothelioma (MPM) are relatively non-specific and of insidious onset, which results both in a delay in the patient seeking medical help, and prolonging the time from presentation to diagnosis (2-3 months). As a result most patients have advanced disease at diagnosis and the prognosis is very poor.

Patients with malignant pleural mesothelioma are typically male and with a median age of 60 years. They will usually present with pleural effusions (evident on a chest x-ray), chest pain and increasing shortness of breath (dyspnoea). This is a result of the diffuse tumour spreading widely into the pleural space surrounding the lung. As pleural effusions accumulate, the tumour thickens to form a rind encasing the lung, which prevents expansion necessary for normal lung function. Dyspnoea is the most common clinical sign of patients with pleural mesothelioma (95% of patients) and can occur at all stages of the disease.

The TNM system is the staging system most commonly used in cancer staging generally. The TNM system describes the extent of the primary tumour (T), the absence or presence of cancer in nearby lymph nodes (N), and the absence or presence of distant metastases (M). Taking these three factors together a stage of disease can be derived:

- Stage I mesothelioma affects one layer of the pleura only. It may have grown into the covering of the pericardium and the diaphragm
- Stage II mesothelioma has spread to both layers of the pleura on one side of the body only
- Stage III mesothelioma has spread to the chest wall, oesophagus or lymph nodes on the same side of the chest
- Stage IV mesothelioma 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

Gradually the tumour infiltrates the surrounding structures and eventually fixes the lung to the diaphragm and intercostal muscles causing severe chest pain. The type of pain will vary depending on the site of the disease: lung invasion causes diffuse visceral pain, chest wall invasion causes localised somatic pain and intercostal nerve involvement or vertebral invasion causes neuropathic pain.

Weight loss, cachexia, night sweats and functional abnormalities such as superior vena cava syndrome, dysphagia, paralysis of the vocal cords and diaphragm may follow this local invasion and death is usually due to compression of the heart and lungs by the tumour mass.

Pemetrexed is a unique, multi-targeted antifolate, which in combination with cisplatin was approved by the EMEA for the treatment of MPM in October 2004. Approval was based upon the results of the largest trial yet performed in MPM for any therapy.

The JMCH study was an international multicenter single-blind, parallel arm, randomised Phase III trial of pemetrexed in combination with cisplatin (pem/cis) versus cisplatin (cis) monotherapy in patients with unresectable MPM who had received no prior chemotherapeutic regimens.

The primary objective of the study was to compare survival in MPM patients treated with pem/cis versus cis monotherapy. Secondary outcomes included time to progressive disease (TTPD), time to treatment failure (TTTF), tumour response rate, duration of response, pulmonary function testing and symptomatic benefit (using Lung Cancer Symptom Scale).

448 patients constituted the intention-to-treat population in JMCH. However, following an amendment in the protocol to include mandatory supplementation with vitamin B_{12} and folic acid, three cohorts (defined by supplementation status) were formed:

- Fully Supplemented (FS) – the patients in this cohort received supplemention with vitamin B_{12} and folic acid for the entire duration of treatment.
- Partially Supplemented (PS) – these were patients who received vitamin B_{12} and folic acid for part of their treatment duration
- Never supplemented (NS) – these were patients who did not receive vitamin B_{12} or folic acid at any time during the treatment duration.

For the purpose of Health Technology Appraisals, additional analyses were performed on a cohort of FS patients who had advanced disease (stage III/IV) at baseline. This cohort reflects the anticipated use of pem/cis in UK clinical practice because:

- Vitamin supplementation with vitamin B_{12} and folic acid is a mandatory part of the pemetrexed licence
- A large majority of MPM patients have advanced (stage III/IV) disease at the time of diagnosis

Since vitamin supplementation is mandated with pemetrexed treatment we have not reported any results for the PS and NS cohorts.

Comparator in study JMCH - Cisplatin

- At the time of the study design, there were no chemotherapy agents licensed for treatment of MPM and there were no established MPM therapy.
- No combination of chemotherapy agent had at that time shown a clinical advantage over a single medicine approach in MPM
- Following discussion with the regulatory bodies it was concluded that cisplatin single-agent was an acceptable comparator for a prospective randomised clinical Phase III trial because:
    - Cisplatin was considered the most active single agent in MPM
    - The contribution of pemetrexed to cisplatin in the management of this disease could be delineated over and above cisplatin alone.

Comparators in the UK – MVP, vinorelbine and Active Symptom Control (ASC/BSC)

Four market research studies showed MVP, vinorelbine (+/- platinum), and ASC/BSC to be the main current treatment options for MPM in the UK. Most patients receiving MVP and vinorelbine are doing so as part of a clinical trial.

A systematic review of the literature commissioned by Cancer Care Ontario was adapted and updated by Lilly in order to identify clinical evidence supporting use of these UK comparators.

The results showed there are no phase III trials investigating either of these treatment regimens. Two trials on MVP were found and two on vinorelbine (+/- platinum). Three of the trials were non-comparative phase II based on small patient numbers while the fourth was a non-comparative, prospective case series with 150 mesothelioma patients. Evidence on ASC/BSC is equally limited with only one UK specific reference found, and three non-UK based case series.

The efficacy results for the ITT, FS and FS advanced cohorts are given below.

Efficacy Results from JMCH

	ITT N=448		FS n=331		FS (advanced) n=247	
	Pem/cis n=226	Cis n=222	Pem/cis n=168	Cis n=163	Pem/cis n=125	Cis n=122
Survival	12.1	9.3	13.3	10.1	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
p-value	0.020		0.051		0.003	
HR	0.77		0.75		0.63	
TtPD	5.7	3.9	6.1	3.9	5.6	3.0
p-value	0.001		0.008		<0.001	
TtTF	4.5	2.7	4.7	2.7	4.4	2.6
p-value	0.001		0.001		<0.001	
RR	41.3	16.7	45.5	19.6	43.5	16.4
p-value						

QoL and symptom benefits

Patients were assessed using the Lung Cancer Symptom Scale (LCSS-meso), and advantages for pem/cis were seen. Pem/cis patients showed most significant improvements in breathlessness and pain – the most common and debilitating symptoms in MPM. Differences between arms for ITT, FS AND FS (adv) over time were investigated by using the AUC method, and all parameters (pain, dyspnoea, fatigue, anorexia, cough and global QoL) became significantly improved in favour of pem/cis as treatment continued. Pulmonary function in pem/cis treated patients improved consistently in comparison to those treated with cis alone, with significant improvements seen in SVC, FVC and FEV_1, as a percentage of predicted normal. Greatest differences occurred by the end of treatment (cycle 6).

Safety data from JMCH for the FS cohort

Summary of maximum Common Toxicity Criteria grade 3 or 4 toxicities (FS cohort)

	Pem/cis (N=168)		Cisplatin (N=163)		
	No. of patients	%	No. of patients	%	*p* value
Haematologic laboratory toxicity					
Haemoglobin	7	4.2	0	0	0.015
Leukocytes	25	14.9	1	0.6	<0.001
Neutrophils	39	23.2	5	3.1	<0.001
Platelets	9	5.4	0	0	0.004
Non-laboratory toxicity					
Nausea	20	11.9	9	5.5	0.051
Fatigue	17	10.1	15	9.2	0.853
Vomiting	18	10.7	7	4.3	0.036
Diarrhea	6	3.6	0	0	0.030
Dehydration	7	4.2	1	0.6	0.067
Stomatitis	5	3.0	0	0	0.061
Anorexia	2	1.2	1	0.6	–
Febrile neutropenia	1	0.6	0	0	–
Infection with G3 or G4 neutropenia	0	0	0	0	–
Rash	1	0.6	0	0	–

Pem/cis compared to current practice in the UK

The following tables present the clinical results for MVP, vinorelbine and ASC from the citations identified in the systematic search. Results for pem/cis and cisplatin are for the fully supplemented cohorts from JMCH. The FS population results were used because this reflects use in all patients treated with pemetrexed and would enable a fair comparison versus the comparators used in UK clinical practice.

Reported Survival Outcomes for pem/cis (FS) and UK comparators in MPM

	Pem/cis[1]	Cis[1]	MVP [2/3]	Vin[4]	Vin+Oxa[5]	ASC[6]
Number of patients	168	163	39/150	29	26	191
Median survival (months)	13.3	10.0	6/7	10.6	8.8	7
Response rate (%)	45.5	19.9	20.5/15.3	24	23	NR
Phase III trial	Yes	Yes	No	No	No	No

1. Vogelzang 2003 2. Middleton, 1998 3. Andreopoulou, 2004 4. Steele, 2000 5. Fennell, 2005 6. Aziz 2002. NR – not reported. Vin – vinorelbine, Vinb – vinblastine, cis – cisplatin, MVP – mitomycin+vinblastine +cisplatin, oxa – oxaliplatin, ASC – active symptom control, FS – cohort fully supplemented

Grade 3/4 reported toxicities for pem/cis and UK comparators

Haematologic

- Reported Grade 3/4 neutropenia in pem/cis (23%) was comparable with MVP (22%) , vinorelbine + platinum (18%). Steele (2005) reported 62% neutropenia for vinorelbine monotherapy.
- Neutropenic sepsis occurred in 0.6% of pem/cis patients compared to 2% in MVP patients, and 4% in vinorelbine monotherapy trial. Rates of infection were 0% for pem/cis compared to 6% and 12% reported in the two MVP studies. Rates of anaemia were similar in all studies.

Non-laboratory

- There is limited reporting for the non-haematologic toxicities in the literature.
- Nausea and vomiting in pem/cis was reported in 12/11% of patients compared to 8/9% for MVP patients and 12% for vinorelbine + platinum patients

The economic evaluation includes two models:

Model 1 is a model based upon individual patient data (IPD) from registration phase III trial JMCH and calculates the direct health service costs and the incremental survival outcomes associated with pemetrexed plus cisplatin compared to cisplatin monotherapy.

Certain sub-groups were included in the analysis. These patient sub-groups were chosen to closely reflect the anticipated use of pem/cis in UK clinical practice i.e. Full vitamin supplementation with advanced (stage III/IV) disease, and full vitamin supplementation with good (PS 0/1) performance status. These patient sub-groups are large patient groups that represent 75% and 86% of the full FS trial population respectively.

Model 2 compares the costs and outcomes for a fully supplemented (FS) pem/cis patient to the interventions most commonly used in UK clinical practice. Information for the model inputs used in current practice was found using a systematic review of the literature and a research survey of 15 UK oncologists who treat MPM. Despite the limitations in available data, an economic model was constructed in an attempt to provide a pragmatic comparison of pem/cis with existing therapies in the UK. The results can provide an indication of the level of expected incremental cost and benefit for each treatment comparison and the likely cost-effectiveness of pem/cis in UK clinical practice.

Cost-effectiveness ratios for Model 1 – pem/cis compared to cisplatin

Patient group (number of patients)	Mean survival outcomes		Median survival outcomes	
	Incremental cost/LY	Incremental cost/QALY	Incremental cost/LY	Incremental cost/QALY
Fully Supplemented *(n=331)*	£44,264	£68,598	£34,393	£52,188
FS with Stage III/IV disease *(n=247)*	£35,065	£53,314	£21,948	£35,158
FS with PS 0/1 *(n=284)*	£31,688	£48,099	£27,582	£41,596
FS w AD & PS 0/1 (n=207)	£31,337	£47,567	£19,101	£27,824

Economic analysis of pem/cis compared with cisplatin resulted in higher cost-effectiveness ratios than would be considered to fall entirely within the 'acceptable' range of cost-effectiveness. However, for an innovation in an orphan disease that has no licensed or proven alternative to ASC/BSC, it is important to give special consideration to the benefits that pem/cis can offer to patients with MPM.

Cost-effectiveness ratios for Model 2 – pem/cis (FS) compared to current UK practice

Comparator	Mean survival outcomes	
	Incremental cost/LY	Incremental cost/ QALY
MVP	£14,595	£21,731
Vinorelbine +/- platinum	£18,424	£28,391
ASC/BSC	£21,545	£32,066

Pem/cis has been shown to have acceptable cost-effectiveness when compared to current treatment of patients with MPM in the UK.

Malignant pleural mesothelioma (MPM) is an orphan disease affecting around 1,900 UK patients in 2001 and is expected to rise to around 2900 cases in 2010. 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.

MPM is an occupational disease: Asbestos exposure is an important contributory factor, with a positive history recalled in around 80% of cases.

Pemetrexed/cisplatin is the first chemotherapy regimen licensed in MPM, and clinical comparisons with other agents in relatively poorer powered studies are difficult, however:

- Against the comparator arm of cisplatin alone (found in meta-analyses to be the most active single agent) clear efficacy benefits exist, with modest additional toxicity.
- The three weekly pem/cis combination appears to provide notable efficacy advantages over single agent weekly vinorelbine, with less haematologic toxicity
- Pem/cis demonstrates more activity than MVP, with better efficacy outcomes
- Pem/cis appears to prolong survival when compared to UK derived ASC data.

EXECUTIVE SUMMARY

Abbreviations:

QALY	Quality-adjusted life-year
QoL	Quality of life
SVC	Slow vital capacity
TtPD	Time to progressive disease
TtTF	Time to treatment failure
PFT	Pulmonary function test
pem/cis	Pemetrexed + cisplatin combination therapy
LCSS	Lung Cancer Symptom Scale
LYS	Life-year saved
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in one second
FS	Fully supplemented
MPM	Malignant pleural mesothelioma
ASC	Active symptom control (consists of analgesics, radiotherapy, pleurodesis)
PS 0/1	WHO Performance Status 0 or 1
AD	Advanced (stage III/IV) disease