

pemetrexed 500mg infusion (Alimta®)

No. (192/05)

Eli Lilly

8 July 2005

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Pemetrexed (Alimta®) in combination with cisplatin is accepted for restricted use within NHS Scotland for the treatment of chemotherapy-naïve patients with stage III/IV unresectable malignant pleural mesothelioma.

Pemetrexed in combination with cisplatin prolonged survival compared with cisplatin alone in patients with unresectable malignant pleural mesothelioma. Pemetrexed is the first licensed agent for the treatment of malignant pleural mesothelioma.

Pemetrexed is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. . SMC has not yet received a submission for this indication and therefore cannot currently recommend its use.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

**Pemetrexed 500mg infusion
(Alimta®)**

Licensed indication under review in combination with cisplatin for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Dosing information under review

500mg/m² body surface area on the first day of a 21-day cycle.

UK launch date September 2004

Comparator medications

No other medicines are specifically licensed for treatment of unresectable malignant pleural mesothelioma. Market research commissioned by the company indicated that the majority (>85%) of patients who are given chemotherapy for this condition received a combination regimen. The main regimens include cisplatin plus pemetrexed, cisplatin plus vinorelbine and mitomycin andvinblastine plus cisplatin (MVP).

Cost per treatment period and relevant comparators

Pemetrexed costs £1600 per cycle and cisplatin costs £62 to £74 per cycle, based on body surface areas of 1.6 to 1.8 m², with costs from the 49th British National Formulary.

Summary of evidence on comparative efficacy

Pemetrexed is an antimetabolite that inhibits folate-dependent enzymes, such as thymidylate synthase, thereby disrupting metabolic processes essential for cell replication.

A single-blind trial recruited chemotherapy-naïve adults with malignant pleural mesothelioma and without brain metastases or a second primary malignancy who had a life expectancy of at least twelve weeks and Karnofsky performance score of at least 70. The population in the primary analysis comprised 448 patients who were randomised and received intravenous (iv) cisplatin 75mg/m² body surface area alone or in combination with iv pemetrexed 500mg/m² on the first day of a 21-day cycle. When evidence became available that pemetrexed-related toxicity may be related to folate deficiency, the study protocol was amended during the trial to give patients oral folic acid 350mcg to 1000mcg daily from one to three weeks before chemotherapy till one to three weeks after treatment had stopped, plus intramuscular (im) vitamin B₁₂ 1mg every nine weeks commencing one to three weeks before chemotherapy. The study population included 331, 47 and 70 patients who received complete, partial and no vitamin supplementation, respectively. Patients given complete vitamin supplementation received the regimen specified in the summary of product characteristics (SPC) and results from this subgroup are detailed in the table below.

The primary endpoint, survival time analysed via log-rank test, was significantly greater with pemetrexed plus cisplatin compared to cisplatin alone. Median survival times in the respective groups were 12.1 months and 9.3 months. In the subgroup of 331 patients who received full vitamin supplementation median survival times with the respective treatments

were: 13.3 and 10 months. The between treatments difference in this subgroup, which was not powered to detect this, was of borderline significance ($p=0.051$). In both populations the following secondary endpoints were significantly improved with pemetrexed plus cisplatin compared to cisplatin alone: time to disease progression, time to treatment failure and response rate. These results are detailed in the table below.

Results of trial comparing pemetrexed plus cisplatin versus cisplatin in chemotherapy naïve patients with malignant pleural mesothelioma for all patients randomised and treated and the subgroup of these patients who received full vitamin supplementation.

	Randomised and treated		Full vitamin supplement	
	Pemetrexed / cisplatin	Cisplatin	Pemetrexed / cisplatin	Cisplatin
	n = 226	n = 222	n = 168	n = 163
Median survival (months)	12.1*	9.3	13.3 ^{\$}	10.0
Median time to disease progression	5.7***	3.9	6.1**	3.9
Median time to treatment failure	4.5***	2.7	4.7***	2.7
Response rate (%) [#]	41***	17	46***	20

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$, \$ $p = 0.051$ versus cisplatin; # complete or partial response

The pulmonary function tests, slow vital capacity (SVC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), were significantly improved with pemetrexed plus cisplatin relative to cisplatin when compared using repeated measures analyses.

Patient-assessed quality of life, measured via 100mm visual analogue scales for symptom severity in a modified version of the lung cancer symptom scale (LCSS), were compared using repeated measures analyses. Pemetrexed plus cisplatin, compared to cisplatin alone, was associated with significantly lower least squares mean scores for pain at cycles 3 to 6 and at cycle 6 for dyspnoea and for interference with activity. The clinical significance of these improvements is unknown.

Summary of evidence on comparative safety

Pemetrexed plus cisplatin is associated with more adverse effects than cisplatin alone. The most common grade 3 or 4 adverse effects with the combination regimen were neutropenia, leucopenia, nausea and vomiting. The incidences of these were reduced from 38%, 34%, 31% and 31%, respectively, by the concomitant administration of folic acid and vitamin B₁₂ to 23%, 15%, 12% and 11%, respectively. The most common grade 3 or 4 adverse effects with cisplatin were fatigue, nausea and vomiting, occurring in 9.2%, 5.5% and 4.3%, respectively, of patients in the group who received full vitamin supplementation.

Summary of clinical effectiveness issues

There is no recognised first-line treatment for malignant pleural mesothelioma and no trial has demonstrated superiority of chemotherapy over best supportive care for this disease. Advice from Scottish oncologists indicates that combination regimens currently prescribed include cisplatin plus vinorelbine and MVP. The quality of data on these regimens is limited and requires investigation in larger trials (please see additional information section for details of ongoing trials). The efficacy and safety of pemetrexed plus cisplatin in practice relative to other chemotherapy regimens and to best supportive care are unknown.

Summary of comparative health economic evidence

The comparator within the analysis is cisplatin monotherapy. A survey of Scottish oncologists undertaken by the manufacturer suggests that half of patients would be offered active symptom control, with the majority of the remainder receiving other chemotherapy regimens as part of a clinical trial.

The economic analysis is presented for the subgroup of fully vitamin-supplemented stage III/IV patients. The estimate of median survival under pemetrexed plus cisplatin is 4.8 months greater than that under cisplatin.

Data on quality of life measured within the trial and on grade 3 and 4 toxicities are presented, but not for the stage III/IV subgroup. It is unclear what impact this might have on between- and within-arm quality of life. A common quality of life for both treatment options is assumed, a value of 0.585 being drawn from the non-small cell lung cancer (NSCLC) literature. This yields a net QALY gain of 0.230.

Resource use data are drawn from the trial, but are not presented separately for stage III/IV patients. Pemetrexed plus cisplatin is stated as involving an additional net drug cost of £7,900, and an overall net cost of £8,200 relative to cisplatin monotherapy. This is stated as resulting in a cost effectiveness ratio of £35,600/QALY among fully vitamin-supplemented stage III/IV patients.

Patient and Public involvement

Patient Interest Group Submission: British Lung Foundation, Scotland
Patient Interest Group Submission: Clydebank Asbestos Group

Budget impact

For the purpose of assessing budget impact it was estimated that there are 193 cases of mesothelioma in Scotland in the first year, this rising to 215 by the fifth year. Seventy-five percent of these patients are taken to have advanced disease. Fifty-one percent of those with advanced disease are assumed to be offered chemotherapy in the first year, this rising to 65% by the fifth year. Pemetrexed is assumed to gain an initial market share of 55%, this rising to 70% by the fifth year.

On the basis of an average of six cycles per patients the budget impact of the drug cost is calculated as £408,000 in the first year, rising to £738,000 in 5 years. No other costs or savings are presented within the budget impact section.

Guidelines and protocols

The 2001 British Thoracic Society statement on malignant mesothelioma in the UK notes that most of the available chemotherapeutic agents have been tried in mesothelioma but none has consistently produced a response rate above 20%. Agents consistently reported to produce response rates of 10-20% include doxorubicin, epirubicin, mitomycin, ifosfamide, cyclophosphamide, cisplatin, carboplatin, and antifolates. Combination chemotherapy trials have not demonstrated consistently greater response rates than single agent trials. There are no published randomised studies which show improved survival in patients treated with chemotherapy compared with supportive care. Symptomatic improvement has been reported following chemotherapy, both in patients with and those without demonstrable tumour regression. However, no randomised studies have compared the effects of chemotherapy with best supportive care on symptoms and quality of life.

The National Institute of Clinical Excellence (NICE) is conducting a technology appraisal of pemetrexed for the treatment of malignant pleural mesothelioma, with publication of advice scheduled for August 2006.

Additional information

At the same time as pemetrexed was approved for the indication detailed above, it was also approved for another indication: as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The Scottish Medicines Consortium has not yet received a submission for this indication.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

*This assessment is based on data submitted by the applicant company up to and including **15 July 2005**.*

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Vogelzang NJ, Rusthoven JJ, Symanowski J et al. Phase III Study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21: 2636-44

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British Thoracic Society. Statement on malignant mesothelioma in the United Kingdom. Thorax 2001; 56: 250-65.

European Medicines Agency. European public assessment report for Alimta. www.emea.eu.int/humandocs/Humans/EPAR/alimta/alimta.htm

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