

Resubmission

pemetrexed, 100mg, 500mg powder for concentrate for solution for infusion (Alimta®) No. (531/09)
Eli Lilly and Company Limited

08 May 2009

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

ADVICE: following a resubmission

pemetrexed (Alimta®), in combination with cisplatin, is not recommended for use within NHS Scotland for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

In a planned subgroup analysis of a study comparing pemetrexed plus cisplatin with another platinum-based combination regimen, treatment with pemetrexed plus cisplatin resulted in a small improvement in median survival in patients with a non-squamous histology.

The manufacturer did not present a sufficiently robust economics case to gain acceptance by SMC.

The licence holder has advised their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In combination with cisplatin, for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Dosing information

In combination with cisplatin, pemetrexed 500mg/m² body surface area (BSA) administered as an intravenous (iv) infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75mg/m² BSA infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. See Summary of Product Characteristics (SPC) for pemetrexed and cisplatin for specific dosing advice.

Pemetrexed must be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Product availability date

Licence extension approved 08 April 2008

Summary of evidence on comparative efficacy

Pemetrexed is a multi-targeted anti-cancer agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, the latter a folate-dependent enzyme involved in purine synthesis.

The submitting company has requested that SMC considers the use of this product in a subset of the licensed population comprising only patients with adenocarcinoma histology.

An open-label, randomised non-inferiority study compared pemetrexed/cisplatin with gemcitabine/cisplatin as first-line therapy for advanced non-small cell lung cancer (NSCLC). Previously untreated adult patients had a histologic or cytologic diagnosis of Stage IIIB or IV NSCLC with at least 1 uni-dimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumours criteria, an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 and adequate organ function.

Patients were randomised equally, with adjustments for baseline factors, to a maximum of 6 treatment cycles of 21 days. Treatments were pemetrexed 500mg/m² iv infusion plus cisplatin 75mg/m² iv infusion on day 1, or gemcitabine 1,250mg/m² iv infusion on days 1 and 8 plus cisplatin 75mg/m² iv infusion on day 1. All patients received prior and concomitant medication with folic acid, vitamin B12 and dexamethasone as recommended in the pemetrexed SPC. Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were allowed according to American Society of Clinical Oncology guidelines. Antiemetics could be used. Palliative radiotherapy was permitted for irradiating small areas of painful metastases that could not be managed adequately using systemic or local analgesics.

The primary objective was to compare overall survival (OS) between treatment groups in the intention-to-treat (ITT) population. Non-inferiority would be concluded if the upper bound of the 95% confidence intervals (CI) for the hazard ratio (HR) for OS was <1.176,

corresponding to a 15% lower hazard with gemcitabine/cisplatin than with pemetrexed/cisplatin, and was tested at a one-sided 0.025 alpha level. Secondary objectives included progression-free survival (PFS), time-to-progressive disease, duration of response, time-to-treatment failure and objective tumour response.

The ITT population comprised all 1,725 randomised patients. Approximately 70% were male. Median age was 61 (26 to 83) years. At study entry 24% and 76% of patients had disease stages IIIB and IV, respectively. Approximately 64% had PS 1 and the remainder had PS 0. A median of 5 treatment cycles was administered in each group.

Fifty-three per cent of pemetrexed/cisplatin patients and 56% of gemcitabine/cisplatin patients received post-discontinuation therapies. Seventeen per cent of the pemetrexed/cisplatin group received gemcitabine and 13% of the gemcitabine/cisplatin group received pemetrexed. Approximately 25% of patients in each treatment group received docetaxel and approximately 25% in each treatment group received epidermal growth factor receptor tyrosine kinase inhibitors. The distribution of post-discontinuation therapies in each histologic group was similar to that of the overall study group.

In the ITT population, median OS in the pemetrexed/cisplatin group was non-inferior to that in the gemcitabine/cisplatin group, 10.3 versus 10.3 months; (HR 0.94, 95% CI: 0.84 to 1.05).

The subgroup analysis of OS by treatment group for each histological type was pre-specified but p-values were not adjusted for multiple comparisons. If allowance for multiple testing is made, the difference in OS between patients with adenocarcinoma treated with pemetrexed/cisplatin compared with gemcitabine/cisplatin failed to reach statistical significance: 12.6 versus 10.9 months; (HR 0.84, 95% CI: 0.71 to 0.99)

Table 1: Analysis of median overall survival

Patient group	Median OS (months) (95% CI)		HR (95% CI)	p-value
	Pemetrexed/ Cisplatin	Gemcitabine/ Cisplatin		
All randomised patients (N=1725)	10.3 (9.8-11.2)	10.3 (9.6-10.9)	0.94 (adjusted) (0.84-1.05)	p<0.001 non-inferiority
Patients with squamous histology (N=473)	9.4 (8.4-10.2)	10.8 (9.5-12.1)	1.23 (adjusted) (1.00-1.51)	p=0.050*
Patients with non-squamous histology (N=1252)	11.0 (10.1-12.5)	10.1 (9.3-10.9)	0.84 (unadjusted) (0.74-0.96)	p=0.011*
Patients with adenocarcinoma (N=847)	12.6 (10.7-13.6)	10.9 (10.1-11.9)	0.84 (adjusted) (0.71-0.99)	p=0.03*

*p-values not adjusted for multiple testing

In the ITT population, 1- and 2-year Kaplan-Meier survival rates were 44% and 19%, respectively, for the pemetrexed/cisplatin arm, and 42% and 14%, respectively, for the gemcitabine/cisplatin arm.

The results of other time-to-event endpoints in the ITT population were similar between treatment groups. Pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin in terms of median PFS (ITT population), 4.8 versus 5.1 months; (HR 1.04, 95% CI: 0.94 to 1.15) and in the adenocarcinoma population, 5.5 versus 5.0 months; (HR 0.90, 95% CI: 0.78 to 1.03).

Summary of evidence on comparative safety

In the pivotal study, patients treated with pemetrexed/cisplatin experienced significantly less anaemia, neutropenia, thrombocytopenia, fatigue, pyrexia, febrile neutropenia, alopecia, hypokalaemia, neuropathy, peripheral sensory neuropathy, tinnitus, and epistaxis than those treated with gemcitabine/cisplatin. Eye disorders, acute renal failure, dry skin, and pigmentation disorder occurred in significantly more patients in the pemetrexed/cisplatin group.

Possibly study-drug related serious febrile neutropenia and pyrexia occurred significantly less often, whereas anorexia and acute renal failure occurred significantly more often in the pemetrexed/cisplatin arm compared with the gemcitabine/cisplatin arm.

Key haematologic grade 3 or 4 drug-related toxicities were significantly lower for pemetrexed/cisplatin compared with gemcitabine/cisplatin, (neutropenia, 15% versus 27%; anaemia, 5.6% versus 9.9%, and thrombocytopenia, 4.1% versus 13%, respectively). For pemetrexed/cisplatin versus gemcitabine/cisplatin, drug-related grade 3 or 4 febrile neutropenia and alopecia, were also significantly lower, whereas drug-related grade 3 or 4 nausea (7.2% versus 3.9%), respectively, was higher.

Patients in the pemetrexed/cisplatin arm versus the gemcitabine/cisplatin arm received significantly fewer transfusions (including red blood cells and platelets), 16% versus 29%, respectively. Administration of erythropoietic factors (10% versus 18% respectively) and of granulocyte colony-stimulating factors (3.1% versus 6.1% respectively) was significantly lower in patients who received cisplatin/pemetrexed.

Significantly fewer patients in the pemetrexed/cisplatin arm compared with the gemcitabine/cisplatin arm discontinued treatment due to cerebrovascular accident: (0.1% versus 0.8%).

Summary of clinical effectiveness issues

The licensed indication for pemetrexed/cisplatin excludes patients with predominantly squamous cell histology as sub-group analyses of treatment effect by histology in the pivotal study demonstrated a negative benefit/risk ratio compared with gemcitabine/cisplatin in squamous cell NSCLC.

The submitting company has requested that SMC considers the use of pemetrexed in a subset of the licensed indication population that includes only patients with adenocarcinoma. The diagnosis of adenocarcinoma is challenging. Clinical experts have advised that accurate diagnosis in NSCLC based on tissue histology can be difficult, in part due to the limited reliability of small tissue samples and the common occurrence of mixed tumour types. The diagnostic capability is, however, expected to improve with the introduction of immunocytochemistry techniques.

The Scottish Intercollegiate Guidelines Network recommends a maximum of 4 treatment cycles with a platinum-based combination doublet regimen in the advanced NSCLC population. The pivotal study permitted up to 6 cycles and the median number in each treatment group was 5.

There is no direct clinical evidence comparing pemetrexed/cisplatin with gemcitabine/carboplatin, the most commonly used treatment in Scotland for advanced NSCLC. Indirect comparisons with gemcitabine/carboplatin and with docetaxel/cisplatin suggest that pemetrexed/cisplatin is superior to both comparators in terms of overall survival in the adenocarcinoma population. However, subgroup analyses based on histology type were performed in the pivotal study only and as p-values were not adjusted for multiple comparisons, the results should be seen as hypothesis generating rather than hypothesis testing.

In the pivotal clinical study pemetrexed showed improved tolerability relative to the comparator regimen. Pemetrexed is administered by iv infusion over 10 minutes on the first day only of the treatment cycle. Compared with other first-line chemotherapy options such as gemcitabine, (infusion over 30 minutes on days 1 and 8), pemetrexed may offer organisational and individual benefits, especially for patients who live in rural areas.

Patients receiving pemetrexed require concurrent corticosteroid treatment to reduce the incidence and severity of skin reactions and oral folic acid daily before, during and for 3 weeks after treatment. Patients must also receive an intramuscular injection of vitamin B12 in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter.

Summary of comparative health economic evidence

The manufacturer submitted a lifetime cost-utility analysis Markov model comparing first-line pemetrexed/cisplatin with:

- gemcitabine/cisplatin, as per the study;
- gemcitabine/carboplatin, as per the most common current Scottish practice; and
- docetaxel/cisplatin

for the subgroup of patients identified as having non-small cell lung cancer of the adenocarcinoma histology type.

Effectiveness estimates were based on the pivotal study for the comparison with gemcitabine/cisplatin. For gemcitabine/carboplatin an indirect comparison was made using a previously published study. The hazard ratios in the study for overall survival and time to progression between gemcitabine/cisplatin and gemcitabine/carboplatin were taken to apply transitively to those between pemetrexed/cisplatin and gemcitabine/cisplatin. The pattern of hazard ratios observed between pemetrexed/cisplatin and gemcitabine/cisplatin for the adenocarcinoma subgroup was also assumed for gemcitabine/carboplatin. A similar approach was employed for the comparison with docetaxel/cisplatin.

Utility estimates for the model health states of response, stable disease and disease progression and for key adverse events were derived from a utility valuation survey using standard gamble in 100 members of the UK public.

Resource use and cost estimates for drug administration, adverse events and best supportive care were based on a well- conducted expert survey. In contrast to the study, the maximum number of cycles was set to 4, and a stopping rule of 3 cycles for non-responders

in stable disease was assumed. Non-responders in stable disease were assigned the utility of those in progressive disease. Results were sensitive to these assumptions.

This resulted in pemetrexed/cisplatin being estimated as conferring a gain of 0.07 QALYs at a cost of £1,285 when compared with gemcitabine/cisplatin, resulting in a cost effectiveness estimate of £18,442 per QALY. For the comparison with gemcitabine/carboplatin the anticipated gain was 0.13 QALYs at a cost of £1,927, resulting in a cost effectiveness estimate of £14,887 per QALY. For the comparison with docetaxel/cisplatin the anticipated gain was 0.11 QALYs at a cost of £1,270, resulting in a cost effectiveness estimate of £11,179 per QALY.

The main weaknesses were:

- concern that the difference in OS in patients with adenocarcinoma failed to reach statistical significance in the subgroup analysis of the pivotal study, and results being sensitive to assumptions concerning survival gains;
- a mean of around 2.75 cycles in contrast to more than 4 in the study, this having no apparent significant impact upon outcomes in the model;
- it being questionable whether gemcitabine/cisplatin would confer the anticipated overall survival advantage compared to gemcitabine/carboplatin within the indirect comparison;
- a high degree of uncertainty within the comparison with gemcitabine/carboplatin, with a probabilistic analysis suggesting only a 30% likelihood of cost-effectiveness for a willingness to pay of £20,000 per QALY and only a 45% likelihood of cost-effectiveness for a willingness to pay of £30,000 per QALY.

Given these weaknesses, the economic case was not demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: The Roy Castle Lung Cancer Foundation

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published SIGN 80, a national clinical guideline: Management of patients with lung cancer, in February 2005. It states that chemotherapy with a platinum based combination doublet regimen should be considered in all patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive it. Chemotherapy is not generally recommended for NSCLC patients who are PS 3 or 4. For patients with advanced NSCLC the number of chemotherapy cycles should not exceed 4.

The National Institute for Health and Clinical Excellence published Clinical Guideline 24: The diagnosis and treatment of lung cancer, in February 2005. It states that chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.

Additional information: comparators

The current standard of first-line treatment in patients with advanced disease consists of platinum-based doublet regimens (combination of gemcitabine, vinorelbine, docetaxel, or paclitaxel with cisplatin or carboplatin).

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (£)
Pemetrexed	500mg/m² by intravenous infusion on day 1	1,524	6,095
Cisplatin	75mg/m² by intravenous infusion on day 1		
Paclitaxel †	200mg/m ² on day 1	1,563	6,252
Carboplatin*	690mg on day 1		
Paclitaxel †	175mg/m ² by intravenous infusion on day 1	1,243	4,973
Cisplatin	80mg/m ² on day 2		
Docetaxel	75mg/m ² on day 1	1,107	4,427
Cisplatin	75mg/m ² on day 1		
Gemcitabine	1,200mg/m ² by intravenous infusion on days 1 and 8	961	3,844
Carboplatin **	575mg by intravenous infusion on day 1		
Gemcitabine	1,000mg/m ² by intravenous infusion on days 1, 8 and 15	990	3,961
Cisplatin	100mg/m ² by intravenous infusion on day 1 (4 week cycle)		
Gemcitabine	1,250mg/m ² by intravenous infusion on days 1 and 8	865	3,460
Cisplatin	75mg/ m ² by intravenous infusion on day 1 (3 week cycle)		
Vinorelbine capsules	60 to 80mg/m ² orally on days 1 and 8	568 to 700	2,270 to 2,798
Cisplatin	75mg/m ² on day 1		
Vinorelbine infusion	25 to 30mg/m ² by intravenous infusion on days 1 and 8	364 to 423	1,455 to 1,693
Cisplatin	75mg/m ² on day 1		

Doses are for general comparison and do not imply therapeutic equivalence. Costs accessed from eVadis on 03 March 2009. A body surface area of 1.8m^2 was used for dose calculations. One course was calculated as 4 cycles. Costs for additional vitamin supplements for pemetrexed and corticosteroids for pemetrexed, paclitaxel and docetaxel have not been included. *Paclitaxel/carboplatin combination (doses of both drugs based on Scottish practice): Carboplatin: dose (mg)=target area under the curve (AUC) (mg/ml x min) x [Glomerular Filtration Rate (GFR) ml/min + 25]. Target AUC=6mg/ml.min. GFR used=90 ml/min. ** Gemcitabine/carboplatin combination (doses of both drugs from published paper): Carboplatin target AUC=5mg/ml.min. GFR used=90ml/min.† - Contract prices apply that significantly reduce hospital acquisition costs

Additional information: budget impact

The manufacturer estimated a gross drug cost of £65k in year 1, rising to £1.1 million by year 5. Offsets from reductions in other drug use resulted in a net drug cost of £26k in year 1, rising to £439k by year 5. Note these estimates do not take account of any nationally or locally agreed prices that may be in place for existing treatments therefore the net impact on the medicines budget impact in practice would be considerably greater.

This was based upon 762 non-small cell lung cancer patients being eligible for first-line chemotherapy, rising to 853 by year 5. Given an increasing proportion of adenocarcinoma patients being eligible due to improving specificity of histopathology, this yielded an eligible population of 190 in the first year, rising to 341 by year 5. The market share of 15 patients in year 1 (8%), was assumed to rise to 256 patients by year 5 (75%).

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 20 April 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Scagliotti GV, Parikh P, von Pawel J et al. A randomized phase III trial comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer. *J Clin Oncol* 2008;26:3543-3551

Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.

Zatloukal P, Petruzelka L, Zemanova M et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: A phase III randomized trial. *Lung Cancer* 2003;41:321–331.

The European Medicines Agency (EMA) European Public Assessment Report. Pemetrexed (Alimta®) 08/04/2008 H-C-564-II-09 www.emea.europa.eu