pemetrexed 100mg, 500mg, powder for concentrate for solution for infusion (Alimta®) No. (531/09)

Eli Lilly and Company Limited

15 January 2010

The Scottish Medicines Consortium (SMC) 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 2nd resubmission

pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland in combination with cisplatin for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.

It is restricted to patients in whom histology has been confirmed as adenocarcinoma or large cell carcinoma.

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 an improvement in median survival in patients with a non-squamous (adenocarcinoma plus large cell carcinoma) histology.

Chairman,
Scottish Medicines Consortium

Indication

Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.

Dosing information

Pemetrexed 500mg/m^2 of body surface (BSA) is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The recommended dose of cisplatin is 75mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle.

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation.

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

Product availability date

8 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 the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication namely, non-squamous patients with adenocarcinoma or large cell carcinoma, i.e. the licensed population excluding patients with NSCLC with a histological classification 'not otherwise specified'.

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 one 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 six treatment cycles of 21 days. Treatments were pemetrexed 500mg/m^2 iv infusion plus cisplatin 75mg/m^2 iv infusion on day 1, or gemcitabine 1,250mg/m^2 iv infusion on days 1 and 8 plus cisplatin 75mg/m^2 iv infusion on day 1. All patients received prior and concomitant medication with folic acid, vitamin B_{12} and dexamethasone as recommended in the pemetrexed summary of product characteristics.

Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were allowed according to American Society of Clinical Oncology guidelines. Anti-emetics 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 five 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; (Hazard Ratio [HR] 0.94, 95% CI: 0.84 to 1.05). For patients with adenocarcinoma and large cell carcinoma (the population described in the niche) the median OS was 11.8 months versus 10.4 months respectively; HR 0.81 95% CI 0.70 to 0.94). See table for OS results for other sub-groups.

Table: Analysis of median overall survival for the pivotal study

Patient Group	**Median OS (months) (95% CI)**		**Adjusted hazard ratio (95% CI)**	**p-value* (superiority)**
	Pemetrexed/ cisplatin	**Gemcitabine/ cisplatin**		
All randomised patients (N=1,725)	10.3 (9.8 to 11.2)	10.3 (9.6 to 10.9)	0.94 (0.84 to 1.05)	p=0.259 p<0.001 (non-inferiority)
Patients with non-squamous histology (adenocarcinoma + large cell) (N=1,000)	11.8 (10.4 to 13.2)	10.4 (9.6 to 11.2)	0.81 (0.70 to 0.94)	p=0.005
Patients with non-squamous histology (including NSCLC-NOS) (N=1,252)	11.0 (10.1 to 12.5)	10.1 (9.3 to 10.9)	0.84 (0.74 to 0.96)	p=0.011
Patients with adenocarcinoma (N=847)	12.6 (10.7 to 13.6)	10.9 (10.1 to 11.9)	0.84 (0.71 to 0.99)	p=0.03
Patients with large cell carcinoma (N=153)	10.4 (8.6 to 14.1)	6.7 (5.5 to 9.0)*	0.67 (0.48 to 0.96)	p=0.03

Patients with NSCLC-NOS (N=252)	8.6 (6.8 to 10.2)	9.2 (8.1 to 10.6)	1.08 (0.81 to 1.45)	p=0.586

* p values not adjusted for multiple testing. NSCLC-NOS = non-small cell lung cancer-not otherwise specified.

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. In the adenocarcinoma plus large cell carcinoma population PFS was 5.3 versus 4.7 months; HR 0.90, 95% CI: 0.79 to 1.02.

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 in the pemetrexed/cisplatin arm compared with the gemcitabine/cisplatin arm, whereas anorexia and acute renal failure occurred significantly more often. 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 pemetrexed/cisplatin.

The analysis of safety by histology sub-groups was consistent with the safety profile observed in the total population.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication, non-squamous patients with adenocarcinoma or large cell carcinoma i.e. the licensed population excluding ‘not otherwise specified’ patients. The study was not powered for this planned subgroup analysis, and p-values were not adjusted for multiple comparisons, however if allowance for multiple testing is made, the difference in OS in patients with adenocarcinoma and large cell carcinoma (the population described in the niche) treated with pemetrexed/cisplatin compared with gemcitabine/cisplatin remains statistically significant.

The Scottish Intercollegiate Guidelines Network recommends a maximum of four treatment cycles with a platinum-based combination doublet regimen in the advanced NSCLC population. The pivotal study permitted up to six cycles, the median number in each treatment group was five and the mean number of cycles was approximately 4.4.

There is no direct clinical evidence comparing pemetrexed/cisplatin with gemcitabine/carboplatin, the most commonly used treatment in Scotland for advanced NSCLC.

In the pivotal clinical study pemetrexed showed improved tolerability relative to the comparator regimen. Pemetrexed is administered by intravenous 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 three weeks after treatment. Patients must also receive an intramuscular injection of vitamin B_{12} in the week preceding the first dose of pemetrexed and once every three cycles thereafter.

Experts consulted by SMC have advised that histological subtyping is now routinely performed in many parts of Scotland allowing accurate diagnosis of non-squamous NSCLC.

Summary of comparative health economic evidence

The manufacturer submitted a lifetime cost-utility analysis using individual patient data from the 29-month pivotal phase III trial of pemetrexed/cisplatin versus gemcitabine/cisplatin as the basis for extrapolating survival outcomes over a 6 year time horizon. The specific patient population considered in the economic analysis was those with non-small cell lung cancer of the known non-squamous histology type (i.e. adenocarcinoma and large cell carcinoma). The comparators considered were gemcitabine in combination with carboplatin, and gemcitabine in combination with cisplatin.

The gemcitabine/carboplatin combination was considered the primary comparator as it is the most commonly used treatment in Scotland for advanced NSCLC, which was confirmed by clinical experts consulted by SMC.

Estimates of the overall survival benefits of pemetrexed/cisplatin were derived by fitting a parametric survival model to the pivotal trial data for the 29 month duration of the trial and a survival hazard model to extrapolate survival for the additional 43 months beyond the trial. Several survival functions were considered, with the Weibull function considered to represent the most appropriate model. The survival analysis appears robustly performed and provided a good fit to the trial data. Using this analysis pemetrexed/cisplatin was estimated to result in a mean 2.3 month improvement in survival compared to gemcitabine/cisplatin. In the absence of comparative data the same survival outcome was assumed for the primary comparison with gemcitabine/carboplatin. This assumption was supported by a review of meta-analyses comparing cisplatin and carboplatin in NSCLC showing similar survival outcomes associated with either regimen. Clinical experts consulted by SMC also supported this conclusion.

Utility estimates for response, stable and progressive disease states and for adverse event disutilities were derived from a survey using the standard gamble approach in 100 members

of the UK public. A QALY gain of 0.1653 per patient for pemetrexed/cisplatin over the comparators was estimated.

The acquisition costs of pemetrexed/cisplatin and gemcitabine/cisplatin were stated as being based on actual doses used in the trial, representing a mean duration of 4.38 and 4.35 cycles respectively. This may overestimate the actual doses used in practice. The dose for gemcitabine/carboplatin was based on that applied in a recent NICE technology appraisal of pemetrexed for first line treatment of NSCLC. Pemetrexed/cisplatin had the highest drug acquisition costs and gemcitabine/cisplatin had the highest costs associated with drug administration. Other items of resource use were estimated from the literature, guidelines or using expert opinion.

Pemetrexed/cisplatin was associated with an estimated incremental healthcare cost of £2,200 over gemcitabine/carboplatin and £2,750 over gemcitabine/cisplatin. The incremental cost per QALY gained was £13,434 for pemetrexed/cisplatin versus gemcitabine/carboplatin and £16,636 versus gemcitabine/cisplatin. The results were robust to a number of one-way sensitivity analyses performed, including varying the survival benefit of pemetrexed/cisplatin or gemcitabine/carboplatin or cisplatin. The most pessimistic scenarios of a 20% reduction in survival benefit for pemetrexed/cisplatin or a 20% survival improvement for gemcitabine/carboplatin resulted in cost per QALY gained estimates of £41,126 and £30,327 respectively, but all other sensitivity analyses on efficacy, treatment duration, cost and shorter time horizons produced cost per QALY gained ratios below £30,000. Cost-effectiveness based on the time horizon of the trial (29 months) was estimated at £18,459 per QALY gained. Taking drug wastage into account slightly improved the base case cost-effectiveness ratio for pemetrexed/cisplatin (£10,746 versus gemcitabine/carboplatin) as gemcitabine was estimated to have a greater level of wastage per vial than pemetrexed.

Overall, the economic analysis was sufficiently robust for the economic case for pemetrexed/cisplatin in NSCLC patients with adenocarcinoma or large cell carcinoma histology sub-types to have been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from:

- Roy Castle Lung Cancer Foundation

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) 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 Stage IIIB and IV 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 Performance Status 3 or 4. For patients with advanced NSCLC the number of chemotherapy cycles should not exceed four. There is a note on the SIGN website that a need for an update is currently being considered.

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 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). Experts consulted by SMC have advised that the combination gemcitabine/carboplatin is commonly used in Scotland.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (£)
Pemetrexed Cisplatin	**500mg/m^2 iv infusion day 1 75mg/m^2 iv infusion day 1**	**1,512**	**6,048**
Gemcitabine plus platinum			
Gemcitabine Carboplatin	1,200mg/m^2 iv infusion day 1 and 8 575mg/m^2 iv infusion day 1	1,145	4,580
Gemcitabine Cisplatin	1,000mg/m^2 iv infusion day 1, 8 and 15 100mg/m^2 iv infusion day 1 (4-week cycle)	970	3,880
Gemcitabine Cisplatin	1,250mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion day 1 (3-week cycle)	788	3,152
Paclitaxel plus platinum			
Paclitaxel Carboplatin	200mg/m^2 iv infusion day 1 690mg iv infusion day 1	1,277	5,108
Paclitaxel Cisplatin	175mg/m^2 iv infusion day 1 80 mg/m^2 iv infusion day 2	742	2,968
Docetaxel plus platinum			
Docetaxel Cisplatin	75mg/m^2 iv infusion on day 1 75mg/m^2 iv infusion on day 1	1,095	4,380
Vinorelbine plus platinum			
Vinorelbine cap Cisplatin	60 to 80mg/m^2 orally day 1 and 8 75mg/m^2 iv infusion on day 1	512 to 644	2,058 to 2,576
Vinorelbine iv Cisplatin	25 to 30mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion on day 1	352 to 412	1,408 to 1,648

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 October 2009, BNF edition 58 (September 2009) or MIMs (October 2009). A body surface area of 1.8m^2 was used for dose calculations and one course comprises four cycles. Costs for additional vitamin supplements for pemetrexed and corticosteroids for pemetrexed, paclitaxel and docetaxel have not been included. iv= intravenous.

Additional information: budget impact

The gross drug budget impact of pemetrexed/cisplatin is estimated to be £301k in year 1 rising to £1.4 million by year 5, based on 45 patients (17% of adenocarcinoma and large cell carcinoma patients) expected to receive pemetrexed in year 1 and 206 patients (75% market share) in year 5.

The net drug budget impact after displacement of gemcitabine/carboplatin, gemcitabine/cisplatin and docetaxel/cisplatin is estimated to be £101.7k in year 1 rising to £460.3k by year 5.

Diagnosis of known non-squamous NSCLC may be associated with cost implications in areas of Scotland where routine subtyping is not standard practice at the present time.

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 ***04 December 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 reference was supplied with the submission. The reference shaded grey is additional to the one 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

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