Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

pemetrexed, 100mg, 500mg powder for concentrate for solution for infusion (Alimta) SMC No. (642/10)

Eli Lilly and Company Ltd

10 September 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 full submission

pemetrexed (Alimta) is not recommended for use within NHS Scotland.

Indication under review: monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

In a sub-group analysis of patients with non-squamous NSCLC, progression free survival and overall survival (secondary endpoint) were significantly longer for pemetrexed plus best supportive care (BSC) compared to placebo plus BSC.

However, the manufacturer did not present a sufficiently robust economic case and their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Indication

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Dosing Information

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

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

Product availability date

10 July 2009

Summary of evidence on comparative efficacy

Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolism. The indication under review is for maintenance treatment following first-line treatment with platinum-based chemotherapy, a new approach in the treatment of non small cell lung cancer (NSCLC). SMC has previously accepted pemetrexed for restricted use for the first-line treatment (with cisplatin) of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology and as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.

A multi-centre, randomised, double-blind placebo-controlled study comparing pemetrexed plus best supportive care (BSC) with placebo plus BSC has been conducted in patients with stage IIIB (with pleural effusion or positive supraclavicular lymph nodes, or both) or stage IV non-small cell lung cancer before induction therapy. Patients were required to have not progressed during four doublet chemotherapy induction cycles (cisplatin or carboplatin in combination with gemcitabine, paclitaxel, or docetaxel), have an estimated life expectancy of 12 weeks or more and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were randomised in a 2:1 ratio to pemetrexed 500mg/m^2 given as an intravenous (iv) 10 minute infusion every 3 weeks plus BSC or placebo infusion (sodium chloride 0.9%) every 3 weeks plus BSC and treatment was continued until objective disease progression. Maintenance treatment started between 21 and 42 days (inclusive) of last dose of induction therapy. All patients received vitamin B_{12} and folic acid supplementation and dexamethasone prophylaxis during study treatment. Patients were allowed to receive full supportive care therapies concomitantly during the study.

However, no other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications were permitted while patients were participating in the study.

The primary endpoint was progression free survival (PFS) and was measured from date of randomisation (after completion of induction therapy) to the first date of objective progression of disease or of death from any cause. An independent central review was undertaken to ensure that there was no systematic bias in investigator assessments of progressive disease that would favour one study group with respect to PFS. Secondary endpoints included overall survival (OS) (measured from date of randomisation to date of death from any cause), objective tumour response rates (partial or complete response as defined by Response Evaluation Criteria on Solid Tumours) and disease control rate (partial or complete response or stable disease).

The numbers of patients recruited to the pemetrexed and placebo groups were 441 and 222 respectively. The median PFS was significantly longer in the pemetrexed than the placebo group; 4.3 versus 2.6 months (Hazard Ratio [HR] 0.50, 95% confidence interval [CI] 0.42 to 0.61). Independent review of events confirmed these results. In the non-squamous sub-group (481/663 [73%]) PFS was also significantly longer for pemetrexed than placebo; 4.5 versus 2.6 months (HR 0.44, 95% CI 0.36 to 0.55).

Final OS analysis is available and includes 477 events. There was a significant increase in median OS, a secondary outcome, for pemetrexed than placebo treated patients; 13.4 versus 10.6 months; HR 0.79, 95% CI 0.65 to 0.95, p=0.012. In the non-squamous sub-group OS was also significantly longer for pemetrexed than placebo (15.5 versus 10.3 months; HR 0.70, 95% CI 0.56 to 0.88, p=0.002). Pemetrexed was superior to placebo for objective tumour response rate and disease control rate (see table below).

Table: secondary outcomes of objective tumour response rate and disease control rate for all patients and the non squamous population, in the pivotal study

Outcome	**Pemetrexed plus best supportive care**	**Placebo plus best supportive care**
Objective tumour response rate % (n/N)		
All patients	6.8% (30/441)	1.8% (4/222)
Non-squamous sub-group	7.4% (nr)	1.9% (nr)
Disease control rate % (n/N)		
All patients	52% (228/441)	33% (74/222)
Non-squamous sub-group	58% (188/325)	33% (51/156)

nr=not reported

The Lung Cancer Symptom Scale (LCSS) was completed once per cycle during study treatment and within 30 days of discontinuation. Whilst the overall on-study compliance for completion of assessment on the LCSS was high (81% to 87%), compliance decreased for post-discontinuation visits (48% to 54%). Patients treated with pemetrexed had similar improvement in LCSS scores compared with those receiving placebo. Time to worsening (TWS) of patients reported symptoms from date of randomisation to the first date of worsening were measured. Due to a high rate of censoring, median TWS of haemoptysis was not calculated. Time to worsening of pain and haemoptysis was significantly longer for the pemetrexed than placebo arms but there were no differences in any of the other TWS variables.

Summary of evidence on comparative safety

In the pivotal study 89% of patients on pemetrexed and 84% on placebo reported an adverse event and 66% and 37% of patients respectively had an adverse event that was possibly drug related. Patients receiving pemetrexed experienced significantly more clinically relevant adverse events (AEs) including anaemia, leukopenia, neutropenia, thrombocytopenia, nausea, stomatitis, vomiting, fatigue, anorexia, pyrexia, increased alanine transaminase, increased aspartate transaminase, peripheral sensory neuropathy, rash, and decreased creatinine clearance.

The incidence of admissions to hospital due to drug-related adverse effects was higher in the pemetrexed group than placebo group; 19/441 (4.3%) versus none. A similar proportion of patients received colony stimulating factors (13/441 [2.9%] versus 8/222 [3.6%]. However, significantly more pemetrexed-treated patients required transfusions (42/441 [9.5%] versus 7/222 [3.2%]; p=0·003) and erythropoiesis stimulating agents (26/441 [5.9%] versus 4/222 [1.8%]; p=0·017).

The European Medicines Agency (EMA) commented that overall, the safety results for pemetrexed as a maintenance treatment were consistent with the known safety profile of pemetrexed.

Summary of clinical effectiveness issues

The main aim of maintenance treatment is to 'maintain' the clinical benefit achieved following first-line chemotherapy in order to extend overall survival. Maintenance treatment offers the opportunity for patients to receive active treatment when potentially tumour and symptom burden is low, patient tolerance is high and patients are of good performance status. This is a new approach in the treatment of patients with non-small cell lung cancer and is not current practice in the UK. Pemetrexed as maintenance treatment will require out-patient visits for administration of the 10 minute intravenous infusion every 3 weeks and prescribing of support treatments with vitamin B_{12}, folic acid and dexamethasone. Therefore initiation of pemetrexed maintenance treatment may need to be balanced with factors such as previous toxicities with first-line treatment and the patient's desire for a treatment free interval. Furthermore pemetrexed maintenance treatment may have an impact on service delivery in a patient population who would otherwise be currently receiving best supportive care. Some experts consulted by SMC raised concerns over the loss of pemetrexed as an effective second-line treatment option should pemetrexed be used as maintenance treatment.

In the pivotal study there were significant differences in favour of pemetrexed for the primary endpoint, PFS, and for OS, a secondary endpoint. However, a sub-group population (comprising 73% of study population) only is available to support efficacy in the population defined by the licensed indication (non-squamous NSCLC) and the study may not have sufficient power for these analyses. Following results of other pemetrexed phase III studies that showed that pemetrexed had greater efficacy in the non-squamous population the statistical plan for the current study was updated to include a pre-specified test for treatment by histology interaction and sub-group analyses. Histology was not, however, a stratification factor in the study.

The pivotal study employed a placebo-controlled double-blind design. Furthermore, the use of independent review in 88% of patients provided assurance that there was no systematic bias in investigator assessments of progressive disease that would favour one study group. However there are some limitations with the study with respect to generalisability and outcomes. Firstly, approximately one third of patients were east/west Asians and patients enrolled in the study had an ECOG PS of 0 (39% [261/663]) or 1 (60% [400/663]). These factors may affect the generalisability of the results to a Scottish population eligible for pemetrexed maintenance treatment. Secondly, post-discontinuation systemic treatments were given to 51% (227/441) of patients in the pemetrexed group and 67% (149/222) of patients in the placebo group. The range of treatments patients received may not be representative of treatments used second-line in Scotland for patients with locally advanced or metastatic non-small cell lung cancer. Therefore the OS observed in the study may not be representative of the potential survival benefits of Scottish patients.

The percentage of patients who received post-discontinuation treatments was 53% and 67% in the pemetrexed and placebo groups respectively. However only 18% of patients in the placebo arm went on to receive pemetrexed. It is therefore unclear whether the differences in access to pemetrexed treatment (either as maintenance or second-line use) between the pemetrexed and placebo groups influenced the differences in survival.

The extension to the marketing authorisation under review by SMC excludes patients who have had first-line treatment with a pemetrexed plus cisplatin regimen. A study investigating the use of pemetrexed maintenance therapy following induction therapy with this regimen is currently ongoing. The EMA noted that first-line doublet therapy containing pemetrexed was not included because the results of the first-line study with pemetrexed-cisplatin were not yet available at that time.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing pemetrexed maintenance with a 'watch and wait' strategy where no active treatment was undertaken, in line with the licensed indication. A trial-based economic model was used with a time horizon of 6 years, which was stated to be essentially a lifetime horizon.

The clinical data were based on a subgroup of the main clinical study. Extrapolation was used to estimate differences in overall survival and progression-free survival beyond the observed trial follow-up. The clinical study did not include a quality of life measure that could be easily converted into a QALY so values from the literature were used. The base-case analysis did not make an allowance for adverse event disutility.

Costs for medicines use were based on the main clinical study, assuming no vial wastage in the base-case. The base case assumed patients were treated with a mean of 8 cycles over a maximum of 3 years, as per the clinical study. Supportive care costs were estimated from a UK study from 2004, with assumptions being made about the proportion of the cost that was due to terminal care and the proportion on supportive care prior to this. While the assumptions made did not have a clear basis the sensitivity analysis showed that these were not major determinants of the cost per quality adjusted life year (QALY).

In terms of the results, the added cost over the patient's lifetime was estimated to be £12,265 with pemetrexed maintenance, with a QALY gain of 0.2654. The added cost per QALY gained was £46,216. If a Weibull extrapolation was used instead of an exponential, the cost per QALY increased to £51,358 with results of £47,350 and £46,903 respectively if log logistic or log normal distributions were used. Sensitivity analysis indicated that overall survival was a key driver of the model. If overall survival was decreased by 10% the incremental cost effectiveness ratio (ICER) rose to £64,292. The results were not however sensitive to the duration of treatment; treatment durations of one or two years having little impact on the cost per QALY.

The main concerns were as follows:

- The optimal method for extrapolating survival data was uncertain and this could affect the cost per QALY. The base case results were presented for the exponential method but this had the poorest goodness of fit statistic of four methods that were compared, suggesting the poorest fit to the Kaplan-Meier plot of data observed in the clinical study. In addition, the exponential distribution predicted a very small number of long-term survivors in the pemetrexed arm and while this may not seriously bias the result it raises a question about the plausibility of the chosen extrapolation method when other alternatives were available.
- Key data sources included a literature search for utility values, because no adequate data were collected in the clinical study to estimate QALYs, and a Sheffield study for costs of palliative care from 2004. Due to a lack of background information, there were concerns over whether the Sheffield costs were appropriate to use as a basis for costing, although sensitivity analysis suggested they were not the main drivers of the results. It was also unclear how the study providing utility values was selected and the values were not tested in a sensitivity analysis.
- As noted in the clinical effectiveness section, there was concern from Scottish clinical experts that using this medicine in a maintenance setting may mean it would no longer be an effective second-line option.

In conclusion, the analysis shows that in addition to a comparatively high base case ICER, there are uncertainties in terms of the overall survival with treatment and the results were sensitive to this parameter. As such the economic case was not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was made by Roy Castle Lung Cancer Foundation.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) have published Guideline 80; management of patients with lung cancer in February 2005. The guideline recommends treatment with a platinum based doublet regimen in all patients with stage IIIb/IV NSCLC not suitable for curative resection or radical radiotherapy, and are fit enough to receive it. Second-line treatment with 3-weekly docetaxel should be considered for patients with good performance status. The need for an update is currently being considered.

The National Institute for Health and Clinical Excellence (NICE) has published Clinical Guideline 24: The diagnosis and treatment of lung cancer in February 2005. The guideline recommends a

range of first-line and second-line treatment options for stage IIIb/IV NSCLC depending on patient factors. An update is in progress with a publication date of March 2011.

Neither guideline includes a statement regarding maintenance treatment of NSCLC, although the guidelines predate the licensing of pemetrexed for this indication.

Additional information: comparators

Generally best supportive care would be offered to patients. Erlotinib has recently gained marketing authorisation as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. This indication has not yet been reviewed by SMC therefore erlotinib has not been included as a comparator.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per maintenance course* (£)
pemetrexed	**500mg/m^2 intravenous infusion every 3 weeks**	**1,440**	**8,640**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF edition 59 (March 2010) and based on a body surface area of 1.8m^2. Cost for pemetrexed does not include treatment with vitamin B_{12} and folic acid supplementation and dexamethasone. *A course is based on six cycles; the median number of cycles in the non-squamous population in the pemetrexed arm of the pivotal study.

Additional information: budget impact

The medicines budget impact estimated by the manufacturer was £171k in year 1 rising to £2.46m by year 5. The NHS budget impact, including medicines, administration, second-line chemotherapy, and supportive care was estimated to be £198k in year 1 and £2.84m in year 5.

The number of patients eligible for maintenance treatment was 410 in year 1 falling to 302 by year 5. The manufacturer suggested that the number of patients treated would fall over time because pemetrexed is becoming more widely used as first-line therapy and in the maintenance role it is not currently licensed to follow pemetrexed plus cisplatin.

It was assumed 4% of eligible patients would start on pemetrexed maintenance in 2010 rising to 76% of those eligible by 2010; the patient numbers actually on treatment under this scenario would be 16 in 2010 rising to 230 in 2014.

Scottish clinical experts are cautious about this new treatment approach, therefore these patient numbers may be an overestimate.

References

The undernoted references were supplied with the submission.

Ciuleanu T, Brodowicz T, Zielinski C et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009 Oct 24;374(9699):1432-40. Epub 2009 Sep 18

European Public Assessment Report for pemetrexed. European Medicines Agency (EMA), June 2009.http://www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 13 August 2010.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.