PUBLIC SUMMARY DOCUMENT
Product: Pemetrexed disodium, injection, 500 mg, Alimta®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission requested an Authority required listing for use in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma.

2. Background

The PBAC has considered applications to subsidise pemetrexed for mesothelioma on three occasions, most recently in November 2005. At the November 2005 PBAC meeting, as previously, the PBAC rejected the submission because of unacceptable cost effectiveness. The PBAC acknowledged the severity of the condition and the lack of an effective treatment for mesothelioma. However, even these important factors were insufficient to reverse the PBAC's decision not to recommend the listing of pemetrexed for this patient group. *(See also Public Summary Document for November 2005 meeting).*

3. Registration Status

Pemetrexed, in combination with cisplatin, was registered on 30 June 2004 (500 mg) and 8 November 2007 (100 mg) for the treatment of patients with malignant pleural mesothelioma; and for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer, after prior platinum based chemotherapy.

4. Listing Requested and PBAC's View

Authority required

Use in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma.

It was decided that the descriptor 'pleural' should be removed. This would allow use in patients in whom the initial diagnosis is made following detection of a peritoneal tumour.

5. Clinical Place for the Proposed Therapy

Pemetrexed is an antifolate antineoplastic agent indicated for the treatment of malignant pleural mesothelioma. Malignant pleural mesothelioma is a rare, aggressive, locally invasive cancer with a poor prognosis (median survival between 4 and 12 months).

6. Comparator

The submission nominated cisplatin as the main comparator. This was previously accepted by the PBAC.

7. Clinical Trials

This submission relied on 27-month data for the intend-to-treat population of the same key trial as previously provided (Vogelzang et al 2003), which compared pemetrexed (PMT) 500 mg/m^2 IVI combined with cisplatin 75 mg/m^2 IVI, with cisplatin 75 mg/m^2 IVI, in adult patients with malignant pleural mesothelioma (mean 4.7 cycles of therapy).

The submission also presented data from two open-label studies (Burge et al 2005; Obasaju et al 2007) to demonstrate clinical efficacy and safety outside of the clinical trial setting and reflect experience under the Sponsor's Expanded Access Program.

All trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Vogelzang et al 2003	Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma	J Clin Oncol 2003, 21:2636-2644
Burge et al 2005	Retrospective review of pemetrexed with or without platinum in malignant mesothelioma: The Australian Special Access Scheme experience.	Asia Pacific Journal of Clinical Onclolgy 1:47-52, 2005
Obasaju et al 2007	Single arm, open label study of pemetrexed plus cisplatin in chemotherapy naïve patients with malignant pleural mesothelioma: Outcomes of an expanded access program.	Lung Cancer: 55: 187-194, 2007

8. Results of Trials

The key results were derived from the 27 month data for the intend-to-treat population and were reported as median survival, time to progressive disease (TTPD) and time to treatment failure (TTTF).

Summary of survival time (months), TTPD, and TTTF in ITT population

ITT- 27 months (N=448)	PMT/Cis (95%CI)	Cisplatin (95%CI)	Gain	HR (95%CI)	P
Median overall survival	12.1 (10.0-14.4)	9.3 (7.8-10.7)	2.8 months survival	0.77 (0.61-0.96)	0.020
Mean overall survival	14.1	11.8	2.3 months survival		
TTPD (median)	5.7 (4.9-6.5)	3.9 (2.8-4.4)	1.8 months delay	0.68 (0.59-0.87)	0.001
TTTF (median)	4.5 (3.9-4.9)	2.7 (2.1-2.9)	1.8 months delay	0.61 (0.59-0.86)	0.001

There was a statistically significantly longer median survival (2.8 months), and statistically significant delays in TTPD (1.8 month) and TTTF (1.8 month) associated with the PMT – cisplatin combination treatment.

A bootstrap re-analysis of survival data for the ITT population for pemetrexed/cisplatin versus cisplatin alone suggested that the median survival advantage is approximately 2-3 months [95%CI: 0.2, 5.8]. Given that the mean survival of 2.3 months is included in this confidence interval, and although the mean remains the preferred method for conducting an economic evaluation, the differences between ICER values based on point estimates of mean or median survival may not be meaningfully different in the context of significant uncertainty as reflected by the wide confidence intervals around the median survival of pemetrexed.

The median overall survival and response rates for combination treatment reported in the two supporting observational studies were lower than the results reported in the key trial:

- Median overall survival: 9.9 months (Burge et al. 2005), 10.9 months (Obasaju et al. 2007) versus 12.1 months (Vogelzang et al. 2003).
- Response rate: 27% (Burge et al. 2005), 20.8% (Obasaju et al. 2007) versus 41.3% investigator-determined response rate in Vogelzang et al. 2003.

However, these studies were not comparative and therefore it is difficult to make conclusive statements whether in real life the benefits of PMT/cisplatin combination treatment may differ from those reported in the key trial.

Quality of life data from the pivotal trial (Vogelzang et al 2003) using the Patient Lung Cancer Symptom Scale (LCSS) were presented.

There were statistically significant improvement in fatigue, dyspnea, pain, symptom distress, activity level, and overall LCSS, except for hemoptysis, in the pemetrexed+cisplatin treatment arm. The results suggested that although the global QoL scale did not show significant changes, the total LCSS as an average of all nine items reached a statistically significant difference in favour of pemetrexed by cycle 6.

Neutropenia, leukopenia, and anaemia occurred more frequently in the PMT/cisplatin arm than in the cisplatin alone arm with and without regard to supplemental status ($p<0.001$). When the results for treatment-emergent adverse events (TEAEs) were stratified by supplementation status regardless of drug causality, statistically significantly more fully supplemented patients (i.e. those patients that received folic acid & vitamin B_{12} supplementation for the duration of the trial) in the PMT/cisplatin arm compared to the cisplatin treatment arm experienced neutropenia ($p<0.001$), leukopenia ($p<0.001$), anaemia ($p<0.001$), thrombocytopenia ($p<0.001$), stomatitis ($p<0.001$), diarrhoea ($p=0.026$), and rash ($p<0.001$).

Serious adverse events (SAEs) occurred more frequently in the PMT/cisplatin arm than the cisplatin alone arm (22.6% versus 7.2%, respectively; $p<0.001$). Statistically significantly more patients who received full supplementation in the PMT/cisplatin arm than the cisplatin alone arm experienced an adverse event ($p=0.003$).

Overall, the frequency of Grade 3/4 laboratory toxicity was higher in the PMT/cisplatin arm than in the cisplatin alone arm. Severe toxicity was uncommon in the cisplatin arm, compared to the PMT/cisplatin arm where Grade ¾ neutropenia (2.3% vs 27.9%; $p<0.001$) and Grade 3/4 leukopenia (0.9% vs 17.7%; $p<0.001$) were the most common haematologic toxicities.

Rates of toxicities from the two retrospective studies were lower than those in the key trial in the submission and may have reflected selection of patients in the Expanded Access Program and reliance on investigator-reported SAEs. The most common toxicities were fatigue, dehydration, nausea and vomiting.

9. Clinical Claim

The submission claimed that pemetrexed and cisplatin has significant clinical advantages over cisplatin monotherapy (the comparator) and is significantly more effective than cisplatin monotherapy but more toxic.

For the PBAC's view of this claim, see Recommendations and Reasons.

10. Economic Analysis

An updated preliminary economic evaluation was presented using a cost-effectiveness approach. Pemetrexed costs were based on the assumption of no wastage of PMT (cost based on mg of drug, not vials used) and a mean 4.7 treatment cycles per patient.

The submission calculated a trial-based incremental discounted cost/extra discounted life year gained in the range $45,000 - $75,000 (no wastage). This increases to be in the range $75,000-$105,000 per life year gained when wastage is included.

The submission argued that the combination therapy offers not only a survival benefit but also symptom palliation and this provided a sufficient basis for using life year gained (LYG) as opposed to quality adjusted life year gained (QALY) in the incremental cost-effectiveness ratio.

Existing approaches to measurement of QALYs may not adequately capture the nature of the quality of life/survival trade-off for patients with end stage disease. In other words, QALYs may not capture the trade-offs adequately because of the constant proportional trade-off implicit in the QALY approach.

The PBAC considered that the QALY gained rather than LYG is the appropriate measure for the ICER, taking into account that the divergence between the ICER based on LYG and QALY, although the latter will likely remain higher, may not necessarily be very large. The Committee agreed that in this case the ICER based on LYG and QALY may not be very different, because a relatively small gain in utility following treatment with pemetrexed is required for the cost per QALY to be equal to the cost per LYG.

A modelled economic evaluation was not presented.

See also Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of patients treated would be less than 10,000 in Year 5 of listing.

The estimated net cost to the PBS would be less than $10 M in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of pemetrexed for mesothelioma in combination with cisplatin on the basis of a high but acceptable cost-effectiveness compared with cisplatin monotherapy.

The PBAC noted a decrease in the mean incremental cost/extra life-year gained (ITT 27 months, no wastage, 4.7 mean cycles) in comparison with previous submissions following a decrease in wholesaler margin.

The PBAC considered that the calculations of this ICER correctly used the mean survival gain of 2.3 months not the median of 2.8 months but the differences in these point estimates are not likely to be meaningfully different in the context of significant uncertainty as reflected by the wide confidence intervals around the median survival (95%CI: 0.2 months, 5.8 months), which includes the mean.

The PBAC considered that the QALY gained rather than LYG is the appropriate measure for the ICER. Noting that the ICER based on LYG and QALY may not be very different, because a relatively small gain in utility following treatment with pemetrexed is required for the cost per QALY to be equal to the cost per LYG. In the light of the new quality of life data provided in the submission, this conclusion was considered plausible.

The PBAC considered that patient numbers may have been under-estimated. However, given the likely number of mesothelioma sufferers requiring treatment and that the tumour is uncommon, the numbers are unlikely to vary greatly on published projections.

There was concern regarding wastage which was a significant factor in previous submissions, but the sponsor stated that this was being addressed by the registration by the TGA of a 100 mg vial. The PBAC recommended the listing of pemetrexed in a 100 mg vial for the same indications as currently listed/recommended to reduce wastage.

Recommendation

List a new 100 mg strength with the following restriction

Restriction:	Authority required Mesothelioma in combination with cisplatin. Locally advanced or metastatic non-small cell lung cancer
Maximum quantity:	1 (100 mg)
Repeats:	3

Add the following to the current 500 mg restriction:

Restriction:	Authority required Mesothelioma in combination with cisplatin.
Maximum quantity:	1 (500 mg)
Repeats:	3

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Eli Lilly Australia welcomes the decision by the PBAC to recommend Alimta be placed on Pharmaceutical Benefits Scheme for the treatment of malignant mesothelioma. This is positive news for patients who have been diagnosed with this condition.