

PUBLIC SUMMARY DOCUMENT

Product: Pemetrexed disodium, powder for IV infusion (base), 500 mg, Alimta®

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: November 2005

1. Purpose of Application

This submission sought a Section 85 Authority required listing for use ‘in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma (MPM)’ or, alternatively ‘patients with un-resectable locally advanced or metastatic pleural mesothelioma’.

2. Background

At the November 2004 PBAC meeting the Committee considered two submissions from Eli Lilly Australia for pemetrexed disodium. The application for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after prior platinum based chemotherapy was recommended for listing. However, the application for combination with cisplatin in patients with malignant pleural mesothelioma was deferred to see the effect of lowering the price on the incremental cost-effective ratio.

At the March 2005 meeting the PBAC rejected a submission on the basis of unacceptable cost-effectiveness and uncertainty about the utility weight that would be associated with the survival gain.

3. Registration Status

Pemetrexed in combination with cisplatin, is registered 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.

OR

Authority required

Use in combination with cisplatin for the treatment of patients with un-resectable locally advanced or metastatic malignant pleural mesothelioma.

The PBAC noted that the first restriction mirrored that originally put forward in November 2004, while the second highlighted the subgroup with advanced disease that was the main focus of this submission.

For further comments, see the Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Pemetrexed is an antifolate antineoplastic agent the submission which has been approved, in Australia, for use in combination with cisplatin for the treatment of malignant pleural mesothelioma.

6. Comparator

The submission nominates cisplatin as the main comparator, which the PBAC considered appropriate.

7. Clinical Trials

The re-submission presented (a) updated survival data (i.e. an extra 3 months' data) for the ITT population from the key trial (H3E-MC-JMCH; Vogelzang, NJ et al, 2003) presented in the original submission and (b) new data for fully supplemented patients (low dose folic acid and vitamin B12) with advanced disease (*a post hoc* sub-group analysis).

The re-submission reported the following:

- Clinical results and cost effectiveness analysis of the updated survival of ITT population (Vogelzang et al; World Lung Cancer Conference July 3-7, 2005; Oral Presentation) from the key trial.)
- Clinical results and cost effectiveness analysis for fully supplemented sub-group from the key trial.
- Clinical results (i.e. overall survival, time to progressive disease and response rates) and cost-effectiveness analysis for fully supplemented patients with locally advanced and metastatic (stage III and IV) disease from the key trial.

8. Results of Trials

The results are summarised below:

Comparison of overall survival results by duration of follow-up and sub-group

Trial population	PMT/cisplatin median survival (months)	Cisplatin median survival (months)	HR (95%CI)	p-value
ITT – 27 months (N=448)	12.1	9.3	0.77 (0.61, 0.96)	0.02 *
ITT – 30 months, adjusted (N=448)	12.8	9.0	0.74 (0.60, 0.90)	0.003 †
FS sub-group – 27 months (n=331) ‡	13.3	10.0	0.75 (0.57, 1.00)	0.051 *
FS+AD sub-group – 27 months (n=247)	13.2	8.4	0.63 (0.46, 0.86)	0.0031 *

* Log-rank test; † Chi-square test; ‡ no new data presented in re-submission; PMT = pemetrexed disodium; ITT = intention-to-treat; FS = fully supplemented; AD = advanced disease (Stage III/IV)

The results for overall survival in the ITT population (N=448) indicated a numerical improvement in median survival at 30 months (PMT/cisplatin gain of 3.8 months over cisplatin alone; log-rank p=0.003) compared to that observed at 27 months (gain of 2.8 months; log rank p=0.02). For the sub-group of fully supplemented patients with advanced disease (Stage III/IV), the median overall survival was numerically better in those patients treated with pemetrexed disodium combined with cisplatin (13.2 months) than cisplatin alone (8.4 months; a gain of 4.8 months, log rank p=0.0031).

Median time to progressive disease (TTPD) – FS+AD sub-group after 27 months' follow-up

	Pemetrexed disodium/cisplatin (n=125)	Cisplatin (n=122)
Median (months)	7.3	3.9
95% CI for median	5.2-9.0	2.8-4.5
p-value	0.0001*	

log-rank test; FS = fully supplemented; AD = advanced disease

In fully supplemented patients with advanced disease, the median time to progressive disease (TTPD) was statistically significantly longer for patients treated with PMT/cisplatin than for patients receiving cisplatin alone (7.3 months versus 3.9 months, respectively; p=0.0001).

Best tumour response (independent reviewer-determined) – FS+AD sub-group

	Pemetrexed disodium/cisplatin (n=125)	Cisplatin (n=122)
Number of patients	105	104
Number of responders	48	17
Response rate	45.7%	16.3%
95% CI for response rate	36.0 – 55.7	9.8 – 24.9
Fisher exact p-value	<0.001	

FS = fully supplemented; AD = advanced disease (Stage III/IV)

In fully supplemented patients with advanced disease, the tumour response rate was statistically significantly greater for patients treated with PMT/cisplatin than for patients receiving cisplatin alone (45.7% vs. 16.3%; $p < 0.001$).

Although a number of secondary efficacy outcomes were presented in the original submission (i.e. time to progressive disease (TTPD), duration of tumour response (TR), time to treatment failure (TTTF), tumour response (TR), clinical benefit (CB) response rate, quality of life measures, and pulmonary function tests), only TTPD and TR were reported in the re-submission.

See Recommendations and Reasons for the PBAC's view on the results of trials.

The re-submission presented toxicity data from the key trial for the fully supplemented sub-group of patients with advanced disease (Stage III/IV). The results indicated that fully supplemented patients with advanced disease (Stage III/IV) in the PMT/cisplatin arm experienced more Serious Adverse Events (SAEs) and Treatment-Emergent Adverse Events (TEAEs) than those patients treated with cisplatin alone.

9. Clinical Claim

In this re-submission the therapeutic relativity was not addressed, though the previous submission claimed that pemetrexed had significant clinical advantages over cisplatin ie it was significantly more effective than cisplatin, but had more toxicity.

The PBAC partially accepted this claim.

See Recommendations and Reasons for the PBAC's views.

10. Economic Analysis

The re-submission presented a preliminary (trial-based) economic evaluation using a cost-effectiveness approach. The preliminary economic evaluation in the re-submission differed from that presented in the original submission due primarily to changes in drug costs.

The trial-based incremental discounted cost/extra discounted life-year gained was between \$15,000 to \$45,000 (for fully supplemented patients with advanced disease). This estimate was based on an incremental median life-years gained/patient.

See Recommendations and Reasons for the PBAC's views.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients treated per year would be < 2000 in Year 4 of listing with an estimated financial cost/year to the PBS of < \$10 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC noted that, as had been requested, the re-submission presented updated and adjusted survival data (i.e. an extra 3 months' data) for the ITT population from the key trial (H3E-MC-JMCH) presented in the original submission. However, the re-submission emphasised new data for fully supplemented patients with advanced disease (a sub-group analysis derived from the previous 27-month follow-up dataset). The stated results for overall survival in the ITT population (N=448) indicated a numerical improvement in median survival at 30 months (PMT/cisplatin gain of 3.8 months over cisplatin alone; log rank $p=0.003$) compared to the unadjusted median survival observed at 27 months (gain of 2.8 months; log rank $p=0.02$). For the sub-group of fully supplemented patients with advanced disease (Stage III/IV), the median overall survival was numerically better in those patients treated with pemetrexed disodium combined with cisplatin (13.2 months) than cisplatin alone (8.4 months; a gain of 4.8 months, log rank $p=0.0031$).

The PBAC was concerned about the reliability of the results of the sub-group analysis in patients with advanced disease, given that they appear to be one of the multiple analyses presented in the trial report. The PBAC noted that this indicated that there were multiple post hoc decisions taken about which "potential prognostic factors" should be further analysed and which of these should be compared across the treatment groups of the trial. Thus interpretation of the reported "statistically significant" test for interaction for the advanced disease sub-group was hindered by the multiplicity of exploratory analyses from which this reported test is presented.

On examining the sub-groups that would be excluded from treatment by the requested restriction because they are at Stage I or II of the disease, the PBAC would have to accept that these patients would have a worse overall survival on pemetrexed plus cisplatin than on cisplatin alone. The PBAC considered this was implausible. In addition, this reversal of treatment effect was not supported by the corresponding analysis across the same sub-groups but assessing the outcome of time to disease progression, which although likely to be a more direct reflection of treatment effect, suggested that although achieving a numerically smaller hazard ratio pemetrexed plus cisplatin was more effective than cisplatin alone in patients at Stage I or II of the disease. Thus, in the absence of a convincing basis to conclude that the treatment effect on survival for PMT plus cisplatin over cisplatin alone was enhanced in patients with advanced disease, the PBAC considered the trial's ITT results represented the most scientifically rigorous basis for estimating the magnitude of the treatment effect in this requested sub-group. The issue of restriction of use to advanced disease would require accurate staging of mesothelioma, which is difficult, and involves an element of clinical judgement. This suggested the likelihood of misclassification and disagreement across experts, which was likely to be exacerbated when the result of the assessment determined the patient's eligibility for subsidy to a therapy which was likely to be accepted as therapeutically superior to the current option of cisplatin for the excluded patients. Misclassifications represent a loss of sensitivity and specificity, both of which contribute to reducing any claimed improvement in incremental cost-effectiveness claimed for the targeted sub-group. Thus, the PBAC did not support the proposed targeting of the drug to patients with advanced disease.

A further concern to the Committee was the use of the median survival in the economic evaluation, which favours pemetrexed, as opposed to the mean survival. The PBAC noted that, in principle, the mean is to be preferred for the purposes of an economic evaluation because it describes the overall impact on a per patient basis by calculating the average. The PBAC also noted that most deaths have been captured given the follow-up in this particular dataset and integrating the area between the full Kaplan Meier curves for the two arms of the trial intrinsically relies upon a richer dataset than calculating the difference in medians, which relies on two single point estimates of time estimated from where the respective Kaplan Meier curve crosses the line representing 50% of patients alive. Thus, the PBAC indicated its preference for relying on differences in mean survival rather than differences in median survival, for the purposes of generating the incremental cost-effectiveness ratios.

The PBAC noted that the presented incremental cost per extra life-year gained increased from the base-case of between \$15,000 to \$75,000 (for fully-supplemented patients with advanced disease, using median survival) to between \$45,000 to \$75,000 (for fully-supplemented patients, ITT population, using mean survival). The PBAC considered the latter ratio to be the more plausible, given the concerns indicated above about the sub-group analysis and the use of median survival as opposed to mean survival. The PBAC considered that there was no demonstration of an improvement in quality of life. It was also recalled from its previous consideration in November 2004 that, on average, patients would spend an extra month of the survival period without disease progression or toxicity from the drug. Thus, if this ratio is quality adjusted, assuming a nominal utility of 0.7, as in November 2004, it increases to between \$75,000 to \$105,000.

The PBAC acknowledged the severity of the condition and the lack of an effective treatment for patients with 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. The PBAC therefore rejected the submission because of unacceptable cost-effectiveness.

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

The sponsor questions the approach taken by PBAC to derive QALY. There has been no formal utility study available for PBAC to assume a utility of 0.7. Thus, the cost per quality adjusted life years derived by PBAC is speculative and not accurate.

The sponsor believes that the application submitted to PBAC provided an updated survival data and also a sub-group analysis which clearly demonstrated the survival advantage with pemetrexed.

Eli Lilly Australia is committed to finding a means to provide equitable access to pemetrexed for malignant pleural mesothelioma patients.