PUBLIC SUMMARY DOCUMENT
Product: Pemetrexed, powder for I.V. infusion, 100 mg and 500 mg (base), Alimta®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought an extension to the current Authority Required listing to include first line treatment of non-small-cell-lung cancer (NSCLC) with non-squamous cell histology in combination with cisplatin.

2. Background

The PBAC has not previously considered pemetrexed for first-line treatment of non-small - cell lung cancer.

At the November 2004 meeting, the PBAC recommended an Authority Required listing for pemetrexed for locally advanced or metastatic non-small cell lung cancer, after prior platinum-based chemotherapy, on a cost-minimisation basis compared with docetaxel. Listing was effective from 1 April 2005.

At the November 2008 meeting, the PBAC deferred an application to amend the current listing for pemetrexed in line with changes to the TGA approved indication for NSCLC pending full evaluation of the submission received for the March 2009 PBAC meeting for pemetrexed in first line use. The change to the Product Information limited treatment to patients with advanced or metastatic NSCLC who have histology other than predominantly squamous cell.

3. Registration Status

On 22 September 2008, the approved indications were extended to include:

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

The wording of the second-line indication was also changed as follows:

- As monotherapy, for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology after prior platinum-based chemotherapy.

Pemetrexed is also registered for the following indication:

- In combination with cisplatin, for the treatment of patients with malignant pleural mesothelioma.

4. Listing Requested and PBAC's View

Authority Required

Initial treatment in combination with cisplatin for patients with locally advanced or metastatic non-small cell lung cancer with non-squamous cell histology (adenocarcinoma and/or large cell carcinoma).

Doses greater than 500 mg per metre squared body surface area (BSA) will not be approved for PBS subsidy. The patient's BSA must be provided at the time of the authority approval.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Lung cancer is one of the most common malignancies worldwide with an increasing incidence in Australia. It is the second leading cause of cancer death in men and the third leading cause in women. Almost 80% of lung cancers are classified as NSCLC, with 65% to 75% of cases presenting as locally advanced or metastatic disease.

There are three main histologic classifications of NSCLC, namely squamous cell carcinomas, adenocarcinomas and large cell carcinomas.

Pemetrexed offers an alternative first-line treatment for patients with NSCLC.

6. Comparator

The submission nominated gemcitabine in combination with cisplatin as the comparator. The PBAC agreed that this was the appropriate comparator.

7. Clinical Trials

The submission presented one multi-centre, Phase III, open-label, randomised trial comparing pemetrexed disodium 500mg/m^2 IVI combined with cisplatin 75mg/m^2 IVI, with gemcitabine 1,250mg/m^2 IVI combined with cisplatin 75mg/m^2 IVI in chemo-naive patients with Stage IIIB/IV NSCLC. The basis of the submission was a pre-specified sub-group analysis from this non-inferiority trial.

The study published at the time of the submission is as follows:

Trial/First author	Protocol title	Publication citation
Direct randomised trial		
Scagliotti *et al.* (2008)	Publication: Scagliotti GV, Parikh P, von Pawel J et al. Phase III Study Comparing Cisplatin Plus Gemcitabine with Cisplatin Plus Pemetrexed in Chemotherapy-Naïve Patients with Advanced-Stage Non-Small-Cell Lung Cancer.	Journal of Clinical Oncology. Vol 26 (21) July 20, 2008.

8. Results of Trials

The overall survival results for all randomised patients of the key trial are summarised in the table below.

Summary of overall survival (months) – all randomised patients

	All randomised patients (N=1725)	
	PEM/Cisplatin (n=862)	GEM/Cisplatin (n=863)
Median (95% CI) overall survival (months)	10.3 (9.8, 11.2)	10.3 (9.6, 10.9)
Fixed Margin Method		
Adjusted analysis - Hazard ratio (95%CI)	0.94 (0.84, 1.05)	

Abbreviations: CI = confidence interval; GEM = gemcitabine; HR = hazard ratio; PEM = pemetrexed;

Both the adjusted (HR = 0.94; 95% CI: 0.84 to 1.05) and Cox regressions for the ITT population support the conclusion of noninferiority. The null hypothesis assumed that gemcitabine/ cisplatin would provide a ≥15% reduction in the risk of death over

pemetrexed/cisplatin, corresponding to a fixed margin of 1.176. The submission justified the 15% non-inferiority margin on pragmatic reasons, as a non-inferiority margin of 10% would have required an extra 2300 patients above the 1725 enrolled in the JMDB trial. The non-inferiority margin was accepted by the PBAC.

The overall survival results for all randomised patients by histological subgroups are summarised in the table below:

Overall survival in histological subgroups – all randomised patients

	Median survival - months (95% CI)	**Adjusted HR* (95% CI)**	**Superiority p-value***
Adenocarcinoma & large cell‡ (N=1000)			
PEM/C (n=512)	11.8 (10.4, 13.2)	0.81 (0.70-0.94)	0.005
GEM/C (n=488)	10.4 (9.6, 11.2)		
Adenocarcinoma (N=847)			
PEM/C (n=436)	12.6 (10.7, 13.6)	0.84 (0.71–0.99)	0.033
GEM/C (n=411)	10.9 (10.2, 11.9)		
Large cell (N=153)			
PEM/C (n=76)	10.4 (8.6, 14.1)	0.67 (0.48–0.96)	0.027
GEM/C (n=77)	6.7 (5.5, 9.0)		
Squamous cell (N=473)			
PEM/C (n=244)	9.4	1.23 (1.00–1.51)	0.050
GEM/C (n=229)	10.8		
Unknown or other histology (N=252)			
PEM/C (n=106)	8.6	1.08 (0.81–1.45)	0.586
GEM/C (n=146)	9.2		

Abbreviations: PEM/C = pemetrexed plus cisplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; GEM/C = gemcitabine plus cisplatin

* Adjusted HR and superiority and non-inferiority (NI) p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/ cytopathological).

The Cox adjusted analyses of overall survival by treatment arm for the histology subgroups suggest that, in patients with adenocarcinoma and large-cell carcinoma, pemetrexed/cisplatin resulted in superior overall survival than gemcitabine/cisplatin (HR 0.81; 95% CI: 0.70 to 0.94). In contrast, the analysis for patients with squamous cell carcinoma suggests worse overall survival (1.4 months) when treated with pemetrexed/cisplatin rather than gemcitabine/cisplatin (HR 1.23; 95% CI: 1.00 to 1.51). The treatment-by-histology interaction analysis (p=0.0011) also showed that overall survival for patients with adenocarcinoma and large cell histology was significantly improved on the pemetrexed/cisplatin arm compared with the overall survival for all other patients with adenocarcinoma and large cell or squamous histology.

The results for progression -free survival (PFS) by histologic group, a secondary efficacy outcome, are shown in the table below:

	Median PFS - months (95% CI)	Adjusted HR* (95% CI)	Superiority p-value*
All randomised patients (N=1725)			
PEM/C (n=862)	4.8 (4.6, 5.3)	1.04 (0.94-1.15)	
GEM/C (n=863)	5.1 (4.6, 5.5)		
Adenocarcinoma & large cell (N=1000)			
PEM/C (n=512)	5.3 (4.8, 5.7)	0.90 (0.79-1.02)	
GEM/C (n=488)	4.7 (4.4, 5.4)		
Adenocarcinoma (N=847)			
PEM/C (n=436)	5.5	0.90 (0.78-1.03)	0.125
GEM/C (n=411)	5.0		
Large cell (N=153)			
PEM/C (n=76)	4.5	0.89 (0.65-1.24)	0.499
GEM/C (n=77)	4.2		
Squamous cell (N=473)			
PEM/C (n=244)	4.4	1.36 (1.12-1.65)	0.002
GEM/C (n=229)	5.5		
Unknown or other histology (N=252)†			
PEM/C (n=106)	4.5	1.28 (0.99-1.67)	0.064
GEM/C (n=146)	5.6		

Abbreviations: PEM/C = pemetrexed plus cisplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; GEM/C = gemcitabine plus cisplatin; HR = hazard ratio; N = number of patients per histologic subgroup; n = number of patients per treatment arm; Sup = superiority.
* Adjusted HR and superiority and NI p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/ cytopathological).
† The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.
Source: Table B.6.4, p57 of the submission

The results for PFS by histologic subgroup showed that pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin in patients with adenocarcinoma histology (adjusted HR 0.90, 95% CI: 0.78 to 1.03). However, pemetrexed/cisplatin failed the non-inferiority test in patients with large cell carcinoma (adjusted HR 0.89, 95% CI: 0.65 to 1.24), squamous cell carcinoma (adjusted HR 1.36, 95% CI: 1.12 to 1.65), and unknown/other histology (adjusted HR 1.28, 95% CI: 0.99 to 1.67). The wider confidence intervals may reflect the smaller sample sizes in these specific subgroups.

In the case of tumour response rates (the only other secondary efficacy outcome reported for the histological subgroups), the results of the histological subgroups suggest that, in patients with adenocarcinoma, pemetrexed/cisplatin was superior to gemcitabine/cisplatin. However, tumour response rates in patients with large cell carcinoma histology were not different between patients in the pemetrexed/cisplatin arm compared to patients in the gemcitabine/cisplatin arm.

The proportion of patients with adenocarcinoma and large cell carcinoma experiencing any possibly study-drug related treatment emergent adverse events (TEAEs) was similar between treatment arms. For both treatment arms, the most commonly reported possibly study-drug related TEAEs were anaemia, neutropenia, nausea, vomiting, anorexia, and fatigue. Patients treated with gemcitabine/cisplatin experienced statistically significantly more anaemia, thrombocytopenia, febrile neutropenia, alopecia, and peripheral sensory neuropathy than patients receiving pemetrexed/cisplatin treatment. Patients treated with pemetrexed/cisplatin experienced statistically significantly more conjunctivitis, increased lacrimation, and pigmentation disorder than patients receiving gemcitabine/cisplatin treatment.

In patients with adenocarcinoma and large cell carcinoma histology there were statistically significantly fewer transfusions (i.e. any type of transfusion, red blood cell transfusions and platelets) in patients randomised to pemetrexed/cisplatin treatment than those patients treated with gemcitabine/cisplatin.

In patients with adenocarcinoma and large cell carcinoma histology there were statistically significantly fewer anti-anaemia medications (i.e. erythropoietin/darbepoetin and iron preparations) and G-CSF/GM-CSF administered to patients in the pemetrexed/cisplatin arm than patients randomised to gemcitabine/cisplatin treatment.

For PBAC's view, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed pemetrexed/cisplatin combination chemotherapy is superior in terms of comparative effectiveness over gemcitabine/cisplatin. The PBAC considered pemetrexed combined with cisplatin was non-inferior to gemcitabine combined with cisplatin in the treatment of locally advanced or metastatic non - small cell lung cancer.

The submission also claimed that pemetrexed/cisplatin has better tolerability, has reduced need for supportive treatment, and has a more convenient administration than gemcitabine/cisplatin in the treatment of patients with advanced metastatic NSCLC with adenocarcinoma and large cell carcinoma. The PBAC agreed with this claim, based on the results of Trial JMDB.

For PBAC's views, see Recommendations and Reasons.

10. Economic Analysis

A modelled economic evaluation was presented. The model calculated mean survival for the two treatment arms, pemetrexed/cisplatin and gemcitabine/cisplatin, based on the estimated Weibull survival function, extrapolated for a total of 54 months. Survival, or life years gained was the primary health outcome, however, utilities were applied to the life years gained in sensitivity analyses. Costs were calculated independently of health outcomes, based on resource use during the (30 month) trial period, which are assumed to occur within the first year. The costs included are those associated with the primary chemotherapy agents, premedication, post-discontinuation chemotherapy treatments, transfusion-related costs and resource use associated with serious adverse events and major toxicities.

The submission estimated the base case ICER per Life Year gained (LYG) using the Weibull model to be in the range of $45,000 - $75,000.

Similar results were obtained for the trial-based and calibration model, both based on the 30-month duration of the trial. Extrapolating two years beyond the trial period resulted in a more favourable incremental cost per life year.

The results of the sensitivity analyses indicated that the model is most sensitive to the price of pemetrexed (by changing the price directly, or by changing the assumed body surface area of the cohort) and the incremental survival between treatment arms.

For PBAC's views, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year to be less than 10,000 patients in Year 5 at a financial cost per year to the PBS of less than $10 million in Year 5 of listing. These figures were considered to be understimates given that market share for pemetrexed as first-line chemotherapy is likely to exceed that predicted in the submission.

12. Recommendation and Reasons

The PBAC recommended listing pemetrexed on the PBS for the treatment of locally advanced or metastatic non small cell lung cancer in combination with cisplatin (first-line therapy) on a cost-minimisation basis compared with gemcitabine based on the clinical data presented. The equi-effective doses were considered to be pemetrexed 500 mg/m^2 equivalent to gemcitabine 1250 mg/m^2 each given on a 21 day cycle.

The PBAC did not recommend differentiating treatment based on histology types as the evidence supporting this was insufficient (see below). There was also a great deal of uncertainty concerning the specificity, sensitivity and accuracy of the histology testing and as the economic model was based on diagnosis by histology types there was also uncertainty regarding the economic model. Therefore, a recommendation on the basis of cost-effectiveness for patients with non-squamous cell histology could not be made.

The submission presented one key multi-centre, Phase III, open-label, randomised trial (JMDB) comparing pemetrexed disodium 500mg/m^2 IVI combined with cisplatin 75mg/m^2 IVI, with gemcitabine 1,250mg/m^2 IVI combined with cisplatin 75mg/m^2 IVI in chemo-naive patients with Stage IIIB/IV NSCLC. This non-inferiority trial pre-specified a non-inferior margin of 15%, which the PBAC accepted. Both the adjusted (HR = 0.94; 95% CI: 0.84 to 1.05) and unadjusted (HR = 0.93 (0.83, 1.04) Cox regressions for the ITT population support the conclusion of noninferiority.

The PBAC also agreed that, based on the results of JMDB, pemetrexed/cisplatin treatment generally has a better safety and toxicity profile than gemcitabine/cisplatin treatment, requires fewer supportive therapies and is more conveniently administered.

The basis of the submission was to differentiate eligible patients according to histology. This arose from a number of pre-specified sub-group analyses from JMDB, and which the PBAC did not accept.

The PBAC noted that the Cox adjusted analyses of overall survival by treatment arm for the histology subgroups suggest that, in patients with adenocarcinoma and large-cell carcinoma, pemetrexed/cisplatin resulted in superior overall survival than gemcitabine/cisplatin (HR

0.81; 95% CI: 0.70 to 0.94). However, the PBAC noted that the magnitude of the benefit seems numerically greater for large-cell carcinoma than adenocarcinoma.

In contrast, the analysis for patients with squamous cell carcinoma suggests worse overall survival (1.4 months) when treated with pemetrexed/cisplatin rather than gemcitabine/cisplatin (HR 1.23; 95% CI: 1.00 to 1.51). The treatment-by-histology interaction analysis for pemetrexed/cisplatin over gemcitabine/cisplatin in overall survival was statistically significant (p=0.0011) for patients with adenocarcinoma and large cell histology compared with patients with squamous histology, which lent some support to the submission's claim. However, the PBAC noted that 15% (252) of the patients had unknown or other histology. These patients of unknown or other histology also had a numerically worse outcome on pemetrexed/cisplatin.

Further, in the case of the secondary efficacy outcomes, the PBAC noted that the results reported in the submission for the histological subgroups were mixed. The PBAC noted that, for progression-free survival (PFS) in patients with adenocarcinoma histology, pemetrexed/cisplatin treatment appeared to be noninferior but not superior to gemcitabine/cisplatin (adjusted HR 0.90; 95% CI: 0.78 to 1.03). In patients with large cell carcinoma histology, pemetrexed/cisplatin failed to meet the defined noninferiority criteria (i.e. HR<1.17647) with the upper limit of the 95% confidence interval of the hazard ratio being greater than 1.17647 (adjusted HR 0.89; 95% CI: 0.65 to 1.24).

In the case of tumour response rates (the only other secondary efficacy outcome reported for the histological subgroups), the PBAC noted that the results of the histological subgroups suggest that, in patients with adenocarcinoma, pemetrexed/cisplatin was superior to gemcitabine/cisplatin (superiority p-value: p=0.015). However, tumour response rates in patients with large cell carcinoma histology were not different between patients in the pemetrexed/cisplatin arm compared to patients in the gemcitabine/cisplatin arm (superiority p-value: p=0.960).

The PBAC observed that this lack of consistency of results for each of the histology-defined subgroups across the three types of outcomes analysed in JMDB weakens the claim of treatment effect modification by histology for pemetrexed in this setting. The PBAC noted the arguments in the Pre-Sub-Committee Response and Pre-PBAC Responses that monotherapy randomised trials of pemetrexed in the second-line (JMEI, post hoc subgroup analysis) and maintenance (JMEN, prespecified subgroup analysis) settings of advanced metastatic NCSLC provided subgroup results which were consistent with the claim of treatment effect modification by histology. The PBAC agreed that these data were supportive, including accepting that the nature of the comparisons in these trials (ie pemetrexed used as monotherapy and against other comparators including placebo) helps isolate the claim with respect to pemetrexed, but did not accept that these data were conclusive.

The PBAC noted that the biological plausibility argument was that, although a multi-targeted anti-folate, pemetrexed largely acts by inhibiting thymidylate synthase (TS) and so is likely to be less effective in tumours which tend to overexpress TS (ie. squamous cell carcinomas rather than adenocarcinomas or large cell carcinomas). However, the PBAC noted that pemetrexed shares its pharmacological action on TS with other long-established chemotherapy agents such as 5-fluorouracil and this claimed differentiation of treatment

effect by histology has not been previously observed. In addition, the PBAC considered that the argument that TS overexpression is associated with histology type was weak and largely retro-fitted to "suit" the trial data. The proposal to examine the histology subgroups in JMDB was based on a study published in 2006 involving 56 surgically resected samples (ie in less than Stage IIIA NSCLC) which examined TS levels (TS mRNA in formalin fixed tissue) in adenocarcinomas (30), squamous cell carcinomas (21) and other types (5) of NSCLC. Large cell cancers were not measured and this small study contradicts previous studies which found no association between TS overexpression and histology.

The PBAC particularly noted a concern with the accuracy of the determination of histology type. Two studies (Stang et al., Lung Cancer 2006 and Field et al., JNCI 2004) which looked at the histology of lung cancers at initial diagnosis and a central review diagnosis. The overall agreement between the initial diagnosis and the central review diagnosis was 65% and 71.5 % respectively and, in the Stang et al study, 40% of squamous and adenocarcinoma cases were reclassified. These studies highlighted the difficulties with histological classification. This difficulty of ascertaining and classifying the histology has important implications for the interpretation of the results of the subgroup analyses and also for the implementation of a PBS restriction based on histology. If the treatment effect modification is true, and the accuracy of histology diagnosis is poorer in Australian practice than in the trial, then the effect of misclassification is to reduce the effectiveness of pemetrexed and make its cost-effectiveness less favourable. The existence of unknown and mixed histology types of NSCLC will have the same effects, noting that the proportions of types in the trial broadly reflects Australian epidemiology.

The PBAC was also aware that the impact of accepting the submission's claim of differential pemetrexed effectiveness by histology type would have consequences for other PBS-listed therapies in locally advanced or metastatic NSCLC, including second-line pemetrexed.

The PBAC considered that a systematic review demonstrating treatment effect on the basis of histology for pemetrexed and other drugs could be conducted and that there should be a way of accurately classifying lung cancers before changing treatment algorithms based on a histological classification system. The true factor mediating any treatment effect modification also needs to be identified.

The PBAC considered that the base case of the modelled economic evaluation should not include transfusion-related costs associated with the use of erythropoietin/darbepoetin because the role of these drugs in oncology has not been accepted by the PBAC and is subject to debate in relation to their overall safety profile.

The PBAC noted comments from consumers and a letter from a doctor in support of the listing which noted that, if pemetrexed was listed for this new indication, there would be a change in the overall treatment paradigm for non small cell lung cancer.

Recommendation

PEMETREXED DISODIUM, powder for I.V. infusion, 100 mg and 500 mg (base)
Extend the listing as follows to include:

Restriction: <u>Authority Required</u>

Locally advanced or metastatic non-small cell lung cancer (Stage IIIB and Stage IV) in combination with cisplatin.

Doses greater than 500 mg per metre squared body surface area (BSA) will not be approved for PBS subsidy. The patient's BSA must be provided at the time of the authority approval.

NOTE: No applications for increased maximum quantities for the 500 mg vial will be authorised.

Max. Qty: 1
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

The sponsor disagrees with the PBACs recommendation to list pemetrexed/cisplatin on a cost minimisation basis to gemcitabine/cisplatin for NSCLC as this listing proposed by PBAC falls outside of the current TGA approved indication for pemetrexed. Furthermore, this recommendation is not reflective of the prospective clinical trial data which demonstrated superior overall survival and an improved tolerability profile for the predominantly nonsquamous population compared to gemcitabine, the accepted standard of care. The sponsor is committed to working with the PBAC to enable pemetrexed access as a first line agent for NSCLC patients with predominantly nonsquamous histology.