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

1. Purpose of Application

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

2. Background

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 PBS listing for pemetrexed in line with changes to the TGA approved indication for NSCLC pending full evaluation of the submission for pemetrexed in first line use which the Committee was advised had been received by the Department. The change to the Product Information limits treatment to patients with advanced or metastatic NSCLC who have histology other than predominantly squamous cell.

At the March 2009 meeting, the PBAC recommended an extension to the listing of 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. 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.

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

Locally advanced or metastatic non-small cell lung cancer (Stage IIIB and Stage IV) with predominantly non-squamous cell histology 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.

NOTES: No application for increased maximum quantities for the 500 mg will be authorised.
Definition of "Predominantly": < 10% squamous component (WHO Classification)
Definition of "non-squamous": adenocarcinoma, large cell carcinoma and other NSCLC histologies (that is disease that does not clearly qualify as adenocarcinoma, large cell carcinoma or squamous cell carcinoma).

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 main comparator. This was previously accepted by the PBAC.

7. Clinical Trials

The re-submission presented the same key trial (JMDB) as in the previous submission. Changes had been made to the subgroup analyses presented in the previous submission. The previous submission presented separate data for each of the histological subgroups studied (ie. adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and 'unknown or other' histology NSCLC), but the re-submission *post-hoc* combined the data of the 'unknown or other' histological subgroup with that of the adenocarcinoma and large cell carcinoma subgroups to form one subgroup (ie. non-squamous histology) and compared this result to the non-squamous histology subgroup.

The published trial presented in the re-submission is reproduced below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Scagliotti et al. (2008)	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.

For PBAC's view see Recommendation and Reasons.

8. Results of Trials

The key results are summarised in the table below.

Overall survival in histological subgroups – all randomised patients

	Median (months) (95% CI)	Adjusted HR[a] (95% CI)	Non-inferiority p-value[a]	Superiority p-value[a]
Non-squamous cell[b] (N=1252)				
PEM/C (n=618)	11.0 (10.1, 12.5)	0.84 (0.74, 0.96)	<0.001	0.011
GEM/C (n=634)	10.1 (9.3, 10.9)			
Squamous cell (N=473)				
PEM/C (n=244)	9.36 (8.4, 10.2)	1.23 (1.00, 1.51)	0.663	0.050
GEM/C (n=229)	10.84 (9.5, 12.1)			

Abbreviations: PEM/C = pemetrexed plus cisplatin; GEM/C = gemcitabine plus cisplatin; HR = hazard ratio; mo = months;
[a] 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).
[b] Non-squamous defined as adenocarcinoma, large cell and other.

The median overall survival time was greater with pemetrexed/cisplatin treatment (11.0 months) than with gemcitabine/cisplatin treatment (10.1 months) - a difference of 0.9 months (adjusted HR 0.84, 95% CI: 0.74 to 0.96) in the subgroup analysis of patients with non-squamous cell histology (adenocarcinoma, large cell carcinoma, and 'other' histology).

Progression-free survival (PFS) by histological subgroup – all randomised patients

	Median PFS Months (95% CI)	Adjusted HR[a] (95% CI)	Non-inferiority p-value[a]	Superiority p-value[a]
Non-squamous cell[b] (N=1252)				
PEM/C (n=618)	5.26 (4.7, 5.5)	0.95 (0.84, 1.06)	<0.001	0.349
GEM/C (n=634)	4.96 (4.6, 5.4)			
Squamous cell (N=473)				
PEM/C (n=244)	4.40 (4.1, 4.9)	1.36 (1.12, 1.65)	0.933	0.002
GEM/C (n=229)	5.52 (4.6, 5.9)			

Abbreviations: PEM/C = pemetrexed plus cisplatin; GEM/C = gemcitabine plus cisplatin; HR = hazard ratio; PFS = progression-free survival.
[a] Adjusted HR and superiority and NI p-values from Cox model (as above)
[b] Non-squamous defined as adenocarcinoma, large cell and other NSCLC histologies. Source:

The results for progression-free-survival (PFS) by histologic subgroup showed that pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin in patients with non-squamous histology (adjusted HR 0.95, 95% CI: 0.84 to 1.06).

The summary of the results for the primary and secondary efficacy outcomes by sub-group, presented in the previous submission is shown below.

Outcome	Adjusted HR (95% CI)	Non-inferiority p-value	Superiority p-value
Overall survival			
Adenocarcinoma & large cell carcinoma	0.81 (0.70, 0.94)	<0.001	0.005
Adenocarcinoma	0.84 (0.71, 0.99)	<0.001	0.033
Large cell carcinoma	0.67 (0.48, 0.96)	<0.001	0.027
Unknown or other histology	**1.08 (0.81, 1.45)**	**0.291**	**0.586**
Non-squamous cell carcinoma	0.84 (0.74, 0.96)	<0.001	0.011
Squamous cell carcinoma	1.23 (1.00, 1.51)	0.663	0.05
Progression-free survival			
Adenocarcinoma & large cell carcinoma	0.90 (0.79, 1.02)	<0.001	0.096
Adenocarcinoma	0.90 (0.78, 1.03)	<0.001	0.125
Large cell carcinoma	0.89 (0.65, 1.24)	0.049	0.499
Unknown or other histology	**1.28 (0.99, 1.67)**	**0.74**	**0.064**
Non-squamous cell carcinoma	0.95 (0.84, 1.06)	<0.001	0.349
Squamous cell carcinoma	1.36 (1.12, 1.65)	0.933	0.002

Abbreviations: HR = hazard ratio; CI = confidence interval; NR = not reported in submission or re-submission

There were no new toxicity data presented in the re-submission for all randomised patients. The re-submission presented new subgroup analyses for treatment-emergent adverse events (TEAEs) and laboratory toxicities. The proportion of patients with non-squamous cell carcinoma (N=1213) experiencing at least one possibly study-drug related TEAE was similar between treatment arms (89.7% in the pemetrexed/cisplatin arm vs. 90.6% in the gemcitabine/cisplatin arm; p=0.63).

There were statistically significantly fewer transfusions (p<0.001), red blood cell transfusions (p<0.001), and platelet transfusions (p=0.002) administered to non-squamous cell carcinoma patients in the pemetrexed/cisplatin arm compared to the gemcitabine/cisplatin arm.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed pemetrexed/cisplatin chemotherapy as superior in terms of comparative effectiveness over gemcitabine/cisplatin for first line treatment of non-squamous cell advanced metastatic NSCLC, including the 'Unknown or other histology population'.

The re-submission claimed pemetrexed/cisplatin as having better tolerability, reduced need for supportive treatment, and more convenient administration than gemcitabine/cisplatin in the treatment of patients with non-squamous cell advanced metastatic NSCLC.

At the March 2009 PBAC meeting, the PBAC expressed concerns around the accuracy of histological diagnosis in determining histological sub-types of NSCLC. In order to support the argument that non-squamous histology is distinguishable from squamous histology in patients with NSCLC, the re-submission used five different approaches. These approaches were:

1. Literature review of diagnostic performance of histology sub-groups in NSCLC;
2. Meta-analysis of diagnostic performance of histology sub-groups in NSCLC;
3. Identification of regulatory or reimbursement agencies that accept NSCLC histology sub-groups;
4. Use of histology as the 'gold standard' test in NSCLC;
5. Examination of PBS listings that include a 'test' for initiation of therapy.

To address PBAC's concerns that the treatment of NSCLC patients on the basis of their histological sub-type represented a 'paradigm shift' in the management of these patients, the re-submission conducted a systematic review of prospective, randomised controlled trials or meta-analyses that investigated treatment effect modification by histology with respect to overall survival, progression-free survival, or treatment response.

Overall survival data from a recently published phase III, multicentre, open-label, randomised trial (Gronberg et al. 2009) of pemetrexed/carboplatin versus gemcitabine/carboplatin were pooled with data from the key pivotal trial (JMDB) to obtain a pooled estimate of effect. The re-submission claimed that the results of the meta-analysis clearly indicated that pemetrexed provided improved survival for patients with non-squamous histology when compared to gemcitabine (HR 0.86, 95% CI 0.76 to 0.97, p=0.02).

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented an updated modelled economic evaluation.

The re-submission's economic analysis calculated an incremental cost per QALY gained between $45,000 - $75,000, similar results for the trial-based and calibration model (Steps 1 and 2), both based on the 30 month trial duration. Extrapolating two years beyond the trial period results in a more favourable incremental cost per life year gained of between $15,000 - $45,000. The PBAC considered that although the re-submission's results are numerically different from the previous submission the overall findings are generally consistent with the results of previous submission.

The re-submission also presented a number of sensitivity analyses varying utility weights, costs, and outcomes.

The results of the re-submission's other sensitivity analyses (by varying selected model inputs by ±10%) indicated that the model is most sensitive to changes in 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. This was consistent with the previous submission.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5 (First-line + second-line pemetrexed).

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the key differences from the March 2009 submission were a price decrease for pemetrexed in the first-line setting, 12.5% price decrease for gemcitabine (generic introduction), the requested listing for predominantly non-squamous cell histology rather than adenocarcinoma and large cell only, two base case analyses, an additional

sensitivity analysis that uses a pooled overall survival estimate from the pivotal JMDB trial and the recently published randomised trial by Gronberg et al. (2009), and exclusion of the cost of erythropoiesis stimulating agents from transfusion costs.

The PBAC noted that the key trial (JMDB) remained the same, but changes had been made to the subgroup analyses presented in the previous submission. The previous submission presented separate data for each of the histological subgroups studied (ie. adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and 'unknown or other' histology NSCLC), but the current re-submission *post-hoc* combines the data of the 'unknown or other' histological subgroup with that of the adenocarcinoma and large cell carcinoma subgroups to form one subgroup (ie. non-squamous histology) and compares this result to the non-squamous histology subgroup.

The PBAC noted that in the subgroup analysis of patients with non-squamous cell histology (adenocarcinoma, large cell carcinoma, and 'other' histology), the median overall survival time was greater with pemetrexed/cisplatin treatment (11.0 months) than with gemcitabine/cisplatin treatment (10.1 months) - a difference of 0.9 months (adjusted HR 0.84, 95% CI: 0.74 to 0.96). However, the results presented in the previous submission showed that pemetrexed/cisplatin was neither non-inferior (p=0.291) or superior (p=0.586) to gemcitabine/cisplatin in patients with 'Unknown or other' histology (HR 1.08, 95% CI: 0.81 to 1.45).

Therefore, the PBAC considered that the clinical claim that pemetrexed/cisplatin chemotherapy is superior in terms of comparative effectiveness over gemcitabine/cisplatin for first line treatment of non-squamous cell advanced metastatic NSCLC was supported by data from JMDB trial, based on the primary efficacy outcome (i.e. overall survival).

However, the claim that pemetrexed/cisplatin is more effective than gemcitabine/cisplatin in treating the subgroup of NSCLC patients with 'unknown or other' histology was not reasonable as there appears to be no evidence of a beneficial effect of pemetrexed/cisplatin treatment over gemcitabine/cisplatin in this subgroup of patients. The PBAC considered that the claim that pemetrexed/cisplatin is better tolerated than gemcitabine/cisplatin was reasonable based on the supporting safety data in the re-submission.

Regarding the classification by histology, the PBAC considered that the results of the literature review of individual studies suggest a degree of diagnostic agreement for some histological subtypes but not for others. The results tend to suggest greater diagnostic agreement amongst study pathologists for adenocarcinoma but less diagnostic agreement in the case of large cell carcinoma. The PBAC considered that since the current requested listing for pemetrexed includes use in patients with adenocarcinoma, large cell carcinoma, and 'other' NSCLC histologies (predominantly non-squamous cell histology) the impact of misclassifying patients may be significant. The PBAC also considered that if the 'unknown or other' histology are included in the requested restriction, the Government would be paying a higher cost for these patients who do no better on pemetrexed than gemcitabine. Therefore, a further price decrease may be needed to offset the lack of response for this patient group.

The PBAC noted that a recently published trial of Gronberg et al. (2009) found that there was no difference in median overall survival in patients with non-sqaumous histology (adenocarcinoma and large cell carcinoma) treated with pemetrexed/carboplatin = 7.8 months

compared with gemcitabine/carboplatin = 7.5 months; P = 0.77. This study also reported that multivariate and interaction tests did not reveal any significant associations between histology and survival. The PBAC considered that the results of the systematic review of studies that examined treatment effect modification by histology amongst other NSCLC therapies (a total of 21 systematic reviews and 163 potentially relevant primary studies) did not show any convincing evidence that there was a treatment effect by histology for drugs other than pemetrexed. In the case of pemetrexed, this effect was demonstrable in certain circumstances eg monotherapy, use with cisplatin but not carboplatin.. However, if listing were to be recommended on the basis of predominantly non squamous cell histology, there should be a NOTE specifying use in patients with less than 10% squamous component so that use in mixed tumours is excluded, as these patients did not benefit or did worse on pemetrexed. In addition the inclusion of histology in the first-line listing should flow on to the second-line listing for pemetrexed for NSCLC.

The PBAC noted that the Gronberg et al (2009) trial was excluded from the submission as pemetrexed plus carboplatin is not a TGA approved NSCLC couplet and fewer treatment cycles were permitted in the trial by Gronberg et al (2009) than the key pivotal trial (4 vs. 6 cycles, respectively). However, the PBAC considered that carboplatin would be used in clinical practice but that the costs and clinical implications of switching to carboplatin for first-line use with pemetrexed were not captured in the model. The March 2009 submission previously noted that platinum based therapies are generally considered interchangeable and the decision relating to use of one over the other will be a clinical decision.

The PBAC considered that the ICER between $15,000 - $45,000 /QALY in the model is acceptable, however, is high given the magnitude of the clinical benefit (0.9 months median overall survival time).

The PBAC agreed that the choice of QALY weights were disease specific not treatment specific and were not appropriate. Earlier stage disease was given a lower utility than later stage disease, which lacked face validity and the arbitrary reduction in utility of the gemcitabine treatment had also not been justified. Also, the application of QALY weights in the model as a single value inappropriately assumed that all quality of life is equal, regardless of duration of disease. Further, the model had included cost offsets of G-CSF use with gemcitabine, when such use is not subsidised by the PBS, making it likely that the true ICER per QALY is higher than calculated.

The PBAC considered that the cost-effectiveness was high and uncertain and that further negotiation regarding the price was necessary as the requested listing included patients with ‘unknown or other histology’ who did not benefit from pemetrexed/cisplatin combination. In addition there was uncertainty regarding the use of carboplatin with pemetrexed which needed to be accounted for in the model.

Therefore the PBAC deferred the submission to allow further dialogue with the sponsor on the issues identified above.

Recommendation:
Defer

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 is working to address issues raised by the PBAC to enable subsidised access to pemetrexed as a first line agent for patients with NSCLC.