PUBLIC SUMMARY DOCUMENT
Product: PEMETREXED DISODIUM, powder for I.V. infusion, 100 mg (base) and 500 mg (base), Alimta®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application

The aim of the submission was to address issues raised at the November 2009 PBAC meeting in considering 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.

Consequently, the submission also requested an amendment to the current PBS-listing second-line therapy of pemetrexed for NSCLC to have the same histological definition of NSCLC as that for first line therapy of pemetrexed for NSCLC.

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 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. As the sponsor did not proceed with implementing this recommendation, listing has not taken place.

At the November 2009 meeting, the PBAC deferred a submission seeking extension of the current Authority Required 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. The PBAC noted that the key differences from the March 2009 submission were a price decrease for pemetrexed in the first-line setting, a 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 used 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 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.

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.

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 platinum therapy. 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:
Not for use in patients with more than 10 % squamous histologic component
No applications for increased maximum quantities for the 500 mg vial will be authorized
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 as the main comparator. The PBAC considered that this was an appropriate comparator.

7. Clinical Trials

The submission aimed to address the following clinical issues:

- The impact of pemetrexed for NSCLC (non-squamous histology) on the clinical management algorithm
    - For first line treatment
    - For patients with squamous cell histologies
    - For patients previously treated with platinum based therapies (second line)
- The expected treatment effect when used in combination with carboplatin
- The sensitivity of histology in NSCLC

As per the submission to the November 2009 PBAC meeting, the submission presented three phase III, randomised, controlled trials, studies JMEI (second-line, pemetrexed vs docetaxel), JMDB (first-line, pemetrexed/cisplatin vs gemcitabine/cisplatin) and JMEN (maintenance, pemetrexed vs placebo), to support the efficacy and safety of pemetrexed in locally advanced or metastatic NSCLC patients with non-squamous histology.

For details of published studies refer to the Public Summary Document for pemetrexed for the November 2009 meeting.

8. Results of Trials

The submission stated that the key study (JMDB) powered to demonstrate non-inferiority showed that overall survival for NSCLC patients who received pemetrexed/cisplatin was non-inferior to that of patients received gemcitabine/cisplatin (median OS, 10.3 vs 10.3 months; HR=0.94; 95 % CI: 0.84-1.05).

The submission presented a pre-planned a priori subgroup analysis for study JMDB based on histological type as evidence of a longer overall survival time in patients with non-squamous NSCLC treated with pemetrexed/cisplatin compared to gemcitabine/cisplatin (HR:0.84; 95 %CI: 0.74-0.96; p=0.011). The submission reported this finding was consistent across trials JMEI and JMEN. In contrast, the submission noted that squamous NSCLC patients have a shorter overall survival time on pemetrexed/cisplatin than on gemcitabine/cisplatin (HR:1.23; 95 % CI:1.00-1.51; p=0.05). The submission reported this finding was consistent across trials JMEI and JMEN.

At the November 2009 meeting, 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 treatment and fewer treatment cycles were permitted in the trial by Gronberg et al (2009) than the key trial JMDB (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 submission provided the following reasons for exclusion of the Gronberg et al (2009) trial in the previous submission:

- The primary endpoint of the trial was quality of life, not overall survival.
- The subgroup analyses were retrospective. The authors state that as the analyses were post hoc, the results should be interpreted with caution.
- The trial was powered at 80 % for a two sided significance level of 5 % to detect a difference in health related quality of life (HRQoL) scores, the primary endpoint. The power used in the Gronberg trial to detect overall survival was 36 %. Based on JMDB data and assuming a hazard ratio (HR) of 0.84, 906 events (deaths) were

required to 75 % power to demonstrate a significant difference in survival between the two treatment groups. Therefore, there was insufficient power in the Gronberg trial to detect a statistically robust survival difference between the two treatment groups.

- The study population comprised of patients with an ECOG performance status (PS) of 0-2. Twenty two percent of patients had an ECOG PS=2 and 18 % were aged at least 75 years or older. Therefore, the study population recruited to the Gronberg trial comprised of a higher proportion of older patients and patients with higher PS, which is a significant negative prognostic factor in advanced NSCLC.

The submission further presented an individual patient data meta-analysis (Ardizzoni et al. 2007) comparing efficacy of cisplatin and carboplatin in first line treatment of advanced NSCLC. The submission also conducted subgroup analyses based on age, stage performance status, drug and histology. The submission stated that it conducted a literature review, a meta-analysis and a review of current practice of overseas regulatory and reimbursement agencies to support the argument that non-squamous NSCLC histology (adenocarcinoma, large cell carcinoma and mixed cell types which were not predominantly squamous) could be differentiated from squamous NSCLC histology.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that pemetrexed would provide an additional survival benefit over the current chemotherapy options, with improved tolerability in NSCLC patients with non-squamous histology.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The economic model was presented in two parts:

- a base case model of pemetrexed vs. gemcitabine in the adenocarcinoma and large cell carcinoma NSCLC population; and
- a second analysis of non-squamous histology NSCLC which has incorporated adenocarcinoma, large-cell carcinoma and "other mixed histologies" to the base case model.

The submission stated that the economic evaluation had been adapted from models used in the March 2009 and November 2009 submissions. The ICER was estimated to be in the range $15,000 to $45,000/QALY (excluding wastage), which is similar to the ICER from the November 2009 submission, which was considered by the PBAC to be high given the magnitude of clinical benefit (0.9 months median overall survival). The ICER is estimated to be in the range of $45,000 to $75,000 /QALY per vial basis (i.e. with wastage).

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission stated that overall the assumptions used to estimate the financial implications were the same as those presented to the November 2009 meeting. Amendments to the assumptions presented in the November 2009 submission include

changes in the cost of pemetrexed as outlined above and gemcitabine (taking into account the 12.5 % generic price reduction introduced in 2009). The submission estimated the net additional cost to Government of pemetrexed in the first line setting as being less than $10 million in Year 1 through to Year 5. This estimate includes a reduced use of gemcitabine.

12. Recommendation and Reasons

The PBAC acknowledged there was a clinical need for new treatments for NSCLC and that toxicity was less with pemetrexed than with gemcitabine, which was an important issue in absence of marked improvement in overall survival.

No new clinical trial data were presented. As in the previous submission, the median survival gain was 0.9 months when the unknown or other histology was included with the adenocarcinoma and large cell histology. The PBAC noted that when pemetrexed was used in combination with carboplatin there was no evidence of survival benefit but acknowledged that quality of life may be increased because of less toxicity. The PBAC considered that substitution would take place between cisplatin and carboplatin and noted the response from MOGA which indicated that in current clinical practice the usage of carboplatin versus cisplatin in combination with pemetrexed was approximately equal and was based on clinical judgment. The PBAC considered that a further price reduction would be needed to offset the use of carboplatin as the ICER would increase substantially and exceed the acceptable range. Further, the PBAC considered that even if it was appropriate to limit pemetrexed to use in combination with cisplatin alone that some patients may experience a decreased quality of life and there may also be an increase in the use of resources.

The PBAC considered that the revised economic evaluation including a higher price for pemetrexed did not address the uncertainty of the November 2009 submission with regard to inclusion of patients with 'unknown or other histology' who did not benefit from pemetrexed/cisplatin combination, or the use of carboplatin with pemetrexed which needed to be accounted for in the model. However, it was noted that the sponsor offered a further price reduction for first-line pemetrexed in its Pre-PBAC Response to account for the patients with "other or unknown" histology. The ICER incorporating the price reduction was estimated to be in the range $15,000 to $45,000/QALY (excluding wastage), which is similar to the ICER from the November 2009 submission, which was considered by the PBAC to be high given the magnitude of clinical benefit (0.9 months median overall survival). The ICER is estimated to be in the range of $45,000 to $75,000 /QALY per vial basis (i.e. with wastage).

The PBAC noted there has been no change to the utilities used in the model. In the short minutes from November 2009, the PBAC stated that the choice of QALY weights were disease specific not treatment specific and were not appropriate. The sponsor's Pre-PBAC Response stated that to reduce the uncertainty regarding the utility difference, as part of the sensitivity analysis, ICERs incorporating no difference in utilities were calculated. The ICER for non-squamous patients (including "other histology") was estimated to be in the range $15,000 to $45,000/QALY (excluding wastage), which suggested little effect on the ICER. However, the PBAC noted that the cost-offsets still included G-CSF costs for gemcitabine and there was still uncertainty related to reductions in utility over time, therefore the ICER is likely to be underestimated.

The PBAC therefore rejected the submission on the basis of an unacceptably high and uncertain cost-effectiveness ratio.

Recommendation:
Reject

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 is disappointed with the PBAC's decision. The company has sought to address the PBAC's concerns in several submissions. Lilly is considering its position regarding any future course of action.