PUBLIC SUMMARY DOCUMENT
Product: Erlotinib hydrochloride, film-coated tablets, 25 mg, 100 mg and 150 mg (base), Tarceva®
Sponsor: Roche Products Pty Limited
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission requested a second-line or third-line listing on the PBS for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

2. Background

At the March 2006 meeting, the PBAC rejected a submission seeking an authority required listing for erlotinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy because equi-effectiveness with docetaxel had not been demonstrated and because of uncertain cost-effectiveness in comparison with best supportive care (BSC). The PBAC considered that any re-submission should also present a comparison with pemetrexed. *(See Public Summary Document for March 2006)*

At the November 2006 meeting, the PBAC considered a resubmission which nominated placebo for BSC, docetaxel and pemetrexed as the main comparators. The PBAC rejected this re-submission because of high and uncertain cost effectiveness ratios compared with best supportive care. There was also doubt about the claims for equi-effectiveness between erlotinib and docetaxel and erlotinib and pemetrexed. *(See Public Summary Document for November 2006)*

3. Registration Status

Erlotinib was registered on 30 January 2006 for the "treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy". Erlotinib in combination with gemcitabine is also registered for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

4. Listing Requested and PBAC's View

Authority required

Treatment as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer with a WHO status of 3 or less where:
(1) disease progression has occurred following treatment with docetaxel or pemetrexed; or
(2) treatment with docetaxel and pemetrexed is contraindicated or cannot be tolerated.

OR

Treatment as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer with a WHO status of 3 or less where disease progression has occurred following treatment with docetaxel or pemetrexed;

OR

Treatment as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer with a WHO status of 3 or less where disease progression has occurred following treatment with at least two chemotherapy agents.

For PBAC's view of the requested listing, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Lung cancer is the fifth most commonly occurring cancer in Australia, accounting for about 9% of all new cancer cases. It is the leading cause of death in men and the second leading cause in women. The primary goal of therapy is to palliate symptoms and prolong progression-free and overall survival.

After failure of first-line chemotherapy, additional second-line chemotherapy can be beneficial. There are few therapeutic options available, other than supportive care and palliative radiation, for patients whose disease has progressed following second-line chemotherapy. Therefore, only a minority of these patients receive additional cytotoxic therapy.

Erlotinib is a new oral agent which is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.

6. Comparator

The submission nominated best supportive care as the comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented study BR.21, a prospective, phase III, randomised, multicentre, parallel-group, double-blind, placebo controlled study which compared the safety and efficacy of erlotinib with placebo in 731 stage IIIB or IV non-small cell lung cancer patients who had failed at least one prior chemotherapy regimen, as the pivotal trial. Patients were randomised to receive erlotinib 150 mg daily or placebo until disease progression or unacceptable toxicity.

The reports published at the time of the submission were as follows:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Shepherd FA (Study BR.21)	Erlotinib in previously treated non-small-cell lung cancer.	New England Journal of Medicine 353: 123-132
Tsao M-S (Study BR.21)	Erlotinib in lung cancer - molecular and clinical predictors of outcome.	New England Journal of Medicine 353: 133-144.
Bezjak A (Study BR.21)	Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21.	Journal of Clinical Oncology 24: 3831-3837.

8. Results of Trials

The key result for both the intent-to-treat (ITT) population and the sub-group of patients who had received at least two chemotherapy agents prior to entering BR.21 (the third-line sub-group) showed that erlotinib prolonged median overall survival.

Study BR.21 showed that erlotinib was associated with significantly more rash and diarrhoea compared to placebo, although they were mild to moderate intensity. There was no relevant haematological toxicity reported. The most frequently reported adverse events identified in a review of all other available safety data for erlotinib were consistent with those reported in BR.21.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described erlotinib as having significant advantages in effectiveness over best supportive care but having more toxicity. Previously the PBAC accepted that there were statistically significant clinical benefits of erlotinib over best supportive care regarding all event rates, including overall survival, 12-month survival rate, progression-free survival and overall response rate.

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

10. Economic Analysis

The submission presented an updated trial-based preliminary economic evaluation. Trial-based cost-effectiveness analyses for erlotinib vs. placebo in the ITT and the third-line populations were performed, respectively. The costs included in the evaluation for both populations were drug acquisition costs, hospitalisation costs, subsequent specialist visit costs in a single course, haematology test costs and blood chemistry test costs.

The trial-based incremental discounted cost per extra discounted life-year gained at the end of trial follow-up was estimated to be in the range $75,000 - $105,000 in the ITT and the third-line populations.

The trial-based incremental discounted cost per extra discounted life-year gained at the median trial follow-up was estimated to be in the range $105,000 - $200,000 in the ITT and the third-line populations.

The submission presented an updated modelled economic evaluation. The updated economic model differed from that presented in the previous submissions in the stepped economic evaluation approach and the time horizon of the extrapolated model.

Overall survival was used as the primary outcome measure in the economic evaluation for both the ITT and third-line populations.

The base case modelled incremental discounted cost per extra discounted life-year gained was estimated to be in the range $45,000 - $75,000 for both the ITT population and third-line population.

For PBAC's comments, 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.
The financial cost/year to the PBS (excluding co-payments) was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC considered that any listing should require that the drug be restricted to patients with a WHO performance status of 3 or less and with stage IIIB or IV NSCLC. Further patients should be required to have received prior platinum therapy and reached a point where

further cytotoxic therapy is not an option. It was also considered that erlotinib should not be subsidised in patients with disease progression while on this therapy.

The PBAC noted that the drug acquisition cost of erlotinib in the extrapolated 4-year modelled evaluation was based on the doses and duration of treatment administered in the trial (17.9 weeks) whereas the duration of the treatment benefit is modelled beyond the follow-up period of the trial (70.33 weeks). The PBAC also noted that 42% of the incremental benefit of the drug is accrued during this extrapolation period.. The PBAC did not consider this was plausible because at the conclusion of the study, only 1.2% of the erlotinib cohort and 1.4% of the BSC cohort (ITT) remained progression free. Although a treatment benefit was observed in the trial beyond the treatment period, the continuation of treatment benefit over the entire period of the model was thus considered questionable, given that the median time from progression to death in the literature is 4.2 months after failure of first line treatment. Furthermore, the modelled survival curves appeared not likely to converge, which was also considered implausible.

The PBAC considered that the re-modelling exercise with converging curves for survival gain was more plausible than the initial analysis in the submission. However, the incremental cost-effectiveness ratio per life-year gained was unacceptably high. There was also some concern about the duration of therapy extending beyond 17.9 weeks.

Although the PBAC believed there is a clinical place for erlotinib in the treatment of NSCLC, a further reduction in price would be required to achieve a positive recommendation to list. The PBAC therefore deferred a final decision on the submission to allow negotiation with the sponsor on this issue.

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 has no further comment.