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 2006

1. Purpose of Application

The resubmission requested an authority required listing for erlotinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.

2. Background

At the March 2006 meeting, the PBAC rejected a submission for 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 resubmission should also present a comparison with pemetrexed.

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.

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 disease progression has occurred following treatment with at least one chemotherapy agent.

The PBAC did not comment on the requested restriction.

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 placebo for best supportive care (BSC), docetaxel and pemetrexed as the main comparators. BSC and docetaxel are as previously agreed by the PBAC, and pemetrexed as previously advised by the PBAC.

7. Clinical Trials

The resubmission presented a randomised placebo-controlled trial comparing erlotinib 150mg daily with BSC in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy, until disease progression or unacceptable toxicity was documented.

The resubmission presented an indirect comparison comparing erlotinib (150mg/day) with docetaxel (75mg/m^2) with BSC as the common reference in patients with locally advanced or metastatic NSCLC who have previously received chemotherapy. This was presented in the previous submission.

New trial data from the non-inferiority trial of docetaxel versus pemetrexed (Hanna 2004) were presented in the re-submission for an indirect comparison of erlotinib versus pemetrexed, the new comparator. Data from the erlotinib arm (150 mg/day) in the placebo-controlled trial BR.21 compared with data from the pemetrexed arm (500 mg/m^2) in the docetaxel-controlled trial (Hanna 2004) were presented in this resubmission.

These trials had been published at the time of submission as follows:

Erlotinib versus BSC (randomised head-to-head trial)

Trial/First author	Protocol title	Publication citation
Study BR.21 Shepherd FA et al (2005)	Erlotinib in previously treated non-small cell lung cancer.	The New England Journal of Medicine 353:123-132.
Study BR.21 Tsao MS et al (2005)	Erlotinib in lung cancer-molecular and clinical predictors of outcome.	The New England Journal of Medicine 353:133-144.

Erlotinib versus docetaxel (indirect comparison, BSC as the common reference)

Trial/First author	Protocol title	Publication citation
Dancey et al (2004)	Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of prospective, randomised phase III trial.	Lung Cancer 43: 183-194
Shepherd et al (2000)	Prospective randomised trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.	Journal of Clinical Oncology 18: 2095-2103.
Fossella (2000) (supportive docetaxel study)	Randomised phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell	Journal of Clinical Oncology 18: 2354-62

Trial/First author	Protocol title	Publication citation
	lung cancer previously treated with platinum-containing chemotherapy regimens.	

Erlotinib versus pemetrexed (indirect comparison without *a common reference)*

Trial/First author	Protocol title	Publication citation
Hanna et al (2004)	Randomised phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.	Journal of Clinical Oncology 22 (9): 1589-1597.

8. Results of Trials

The randomised trial of erlotinib versus BSC demonstrated statistically significant clinical benefits of erlotinib over BSC regarding all event rates, including overall survival, 12-month survival rate, progression-free survival and overall response rate.

In the indirect comparison of erlotinib versus docetaxel, there were no statistically significant differences between erlotinib versus docetaxel, although results quantitatively favoured docetaxel such that a survival advantage for docetaxel could not be excluded. The submission presented additional arguments that the results from docetaxel versus. BSC (Shepherd 2000) were not robust.

The indirect comparison of erlotinib versus pemetrexed had no common comparator, and relied on the overlapping 95% confidence interval (CI) for median overall survival and a comparison of point estimates to infer that erlotinib and pemetrexed have similar efficacy.

9. Clinical Claim

The submission described erlotinib as having (i) similar effectiveness and improved quality of life benefits compared with docetaxel, but a toxicity profile which is not associated with the haematological toxicities; (ii) similar effectiveness to pemetrexed and a different toxicity profile; and (iii) significant advantages in effectiveness over BSC but having more toxicity.

The PBAC noted that the first two descriptions were derived from non-randomised comparisons and concluded that this may not be reasonable. The PBAC also considered that the conclusion of similar effectiveness of erlotinib and docetaxel remained unclear. *See Recommendations and Reasons.*

10. Economic Analysis

An updated preliminary economic evaluation was presented. A cost-effectiveness analysis of erlotinib versus BSC was the same as the previous submission. The resubmission presented a cost-consequence analysis of erlotinib versus docetaxel and a cost-minimisation analysis of erlotinib versus pemetrexed was new to this resubmission.

The trial-based incremental cost/extra life year gained was estimated to be in the range $75,000 – $105,000 over BSC.

An updated modelled economic evaluation was presented. The base case modelled incremental discounted cost/extra life-years gained was estimated to be in the range $45,000 – $75,000.

11. Estimated PBS Usage and Financial Implications

The financial net cost/year to the PBS was estimated to be < $10 million in Year 4 of listing assuming erlotinib substitutes for docetaxel, pemetrexed or gemcitabine.

12. Recommendation and Reasons

As in the previous submission, the randomised trial of erlotinib versus BSC demonstrated statistically significant clinical benefits of erlotinib over best supportive care (BSC) regarding all event rates, including overall survival, 12-month survival rate, progression-free survival and overall response rate.

The PBAC noted that the efficacy of erlotinib in the BR.21 trial and docetaxel 75mg/m^2 in Shepherd 2000 trial was indirectly compared for six common endpoints: median overall survival, the proportion of patients alive at one year, median progression-free survival, the proportion of patients progression-free at six months, overall response rate, and median duration of response. The 95% confidence intervals of erlotinib and docetaxel for their respective absolute risk difference against BSC overlap in the proportions of patients with 6-month progression-free survival and overall response rate. There is no statistically significant difference in the12-month survival rates between docetaxel and erlotinib, the difference in the point estimate is around 14% and numerically favours docetaxel. When the underlying differences in the patients' baseline characteristics across the two trials are taken into account, it is difficult to establish the efficacy of erlotinib relative to that of docetaxel. In all, 4 out of 6 outcomes assessed favoured docetaxel. Outcomes measured in BSC arms in both trials were similar but quantitatively favouring BSC in BR.21. The PBAC considered that this may relate to better prognosis for patients in BR.21 where there were fewer patients with stage IV disease, despite the submission claims that more patients in BR.21 had a poorer performance status and were more heavily pre-treated. As previously, the PBAC considered that a survival advantage for docetaxel could not be excluded, despite additional arguments in the submission and stated at the hearing, based on the results for docetaxel in the comparison of docetaxel with pemetrexed in the Hanna 2004 trial.

The indirect comparison of erlotinib versus pemetrexed, using the Hanna 2004 trial had no common comparator, instead it relied on the overlapping 95% CI for median overall survival and a comparison of the point estimates to infer that erlotinib and pemetrexed have similar efficacy. However, the PBAC noted that the lack of a common reference in the comparison between erlotinib and pemetrexed restricted potential statistical analyses on any outcome measures to establish the relative effectiveness of erlotinib versus pemetrexed. The PBAC thus questioned the validity of the conclusion from this distant indirect comparison, especially when the equi-effectiveness of erlotinib versus docetaxel remained in doubt.

The PBAC acknowledged that in some patients, particularly the frail elderly unable to tolerate more toxic therapies, an oral therapy for this disease could represent an advantage. Thus, the principal concern of the PBAC related to the cost-effectiveness comparing erlotinib with best supportive care. Best supportive care (BSC) was also considered a relevant comparator because even those patients able to tolerate intravenous therapy would be very likely to continue therapy with erlotinib for much longer than with either docetaxel or pemetrexed. The number of cycles administered for the latter drugs are limited by toxicity.

The PBAC rejected the submission, mainly 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.

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.