Public Summary Document

Product:	Erlotinib hydrochloride, tablet, 25 mg, 100 mg and 150 mg (base), Tarceva®
Sponsor:	Roche Products Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

To seek an authority required listing on the Pharmaceutical Benefits Scheme (PBS) for erlotinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

2. Background

This drug had not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Erlotinib is registered 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 of patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

The PBAC's view was that any restriction should stipulate use of erlotinib 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.

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 locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

6. Comparator

The submission nominated docetaxel as the main comparator for patients receiving second- or third-line chemotherapy for locally advanced or metastatic non-small cell lung cancer.

The submission also nominated best supportive care as a comparator for patients who do not currently receive second- or third-line chemotherapy. The submission nominated gefitinib as a secondary comparator.

The PBAC agreed that the appropriate comparators were docetaxel and best supportive care (BSC). In addition, another comparator would be pemetrexed, which was listed on a cost-minimisation basis compared with docetaxel and is replacing docetaxel in the market place. The PBAC did not deem it necessary for mutational testing to access erlotinib treatment and thus ruled out gefitinib as a comparator.

7. Clinical Trials

The submission presented a randomised placebo-controlled trial comparing erlotinib 150mg daily with best supportive care (BSC) in patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy, until disease progression or unacceptable toxicity was documented and two indirect comparisons comparing erlotinib (150mg/day) with docetaxel (75mg/m^2) and with gefitinib (250mg/day), with BSC as the common reference in patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

The list of studies that had been published at the time of submission is as follows:

Trial/First author	Protocol/Publication title	Publication citation
Erlotinib vs BSC (randomised head-to-head trial)		
Study BR.21	A randomized, placebo-controlled study of OSI-774 (Tarceva™) in patients with incurable stage IIIB/IV non-small cell lung cancer who have failed standard therapy for advanced or metastatic disease.	
Shepherd FA et al (2005)	Erlotinib in previously treated non-small-cell lung cancer	The New England Journal of Medicine 353:123-132.
Tsao MS et al (2005)	Erlotinib in lung cancer - Molecular and clinical predictors of outcome.	New England Journal of Medicine 353: 133-44.
Erlotinib vs docetaxel (indirect comparison, BSC as the common reference)		
Shepherd (2000)	Prospective randomized trial of docetaxel versus best supportive care in patents with non-small cell lung cancer previously treated with platinum-based chemotherapy.	Journal of Clinical Oncology 18: 2095-103.
Dancey (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 a prospective, randomized phase III trial.	Lung Cancer 43: 183-94.
Docetaxel trials	FDA Medical Review of a New Drug Application (1999). Application Number: NDA 20449/S11. Drug Name: Taxotere® (docetaxel) for injection concentrate: 1-157. FDA Statistical Review of a New Drug Application (1999). Application Number: NDA 20449/S11. Drug Name: Taxotere® (docetaxel) for injection concentrate: 1-23.	

Erlotinib vs gefitinib (Indirect comparison on efficacy, BSC as the common reference)		
ISEL trial	FDA Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document (2005). Drug Name: Iressa® (ZD1839, gefitinib) tables: 1-27	
Gefitinib dose-finding studies (safety data, not placebo-controlled studies)		
IDEAL-1 trial (Fukuoka 2003)	Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. FDA Medical Review of a New Drug Application (2003). Application Number: NDA 21-399. Drug Name: Iressa® (ZD1839) 250mg tablets: 1-129. FDA Statistical Review of a New Drug Application (2003). Application Number: NDA 21-399. Drug Name: Iressa® (ZD1839) 250mg tablets: 1-29.	Journal of Clinical Oncology 21: 2237-46
IDEAL-2 trial (Kris 2003)	Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. FDA Medical Review of a New Drug Application (2003). Application Number: NDA 21-399. Drug Name: Iressa® (ZD1839) 250mg tablets: 1-129. FDA Statistical Review of a New Drug Application (2003). Application Number: NDA 21-399. Drug Name: Iressa® (ZD1839) 250mg tablets: 1-29.	Journal of the American Medical Association 290: 2149-58.

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 comparisons of erlotinib versus docetaxel and gefitinib, erlotinib showed numerically similar effectiveness to docetaxel and superior (statistically significant) evidence for effectiveness over gefitinib for median survival.

The results of the key trials are summarised in the tables below.

Results of the comparative randomised trial BR.21: Erlotinib vs BSC

Outcomes	Erlotinib	BSC	ARD (erlotinib vs BSC) (95% CI)	Hazard ratio (95% CI)
Overall survival	n=488	n=243		
Number (%) of patients who died	378 (77.46)	209 (86.01)	-8.55 (-14.27, -2.82)	NC
Median duration of survival in months (95% CI)	6.67 (5.52, 7.79)	4.70 (4.11, 6.28)	1.97 (0.41, 3.59)	0.73 (0.60, 0.87) p=0.001

Results of the indirect comparisons

Trial	Treatment effect (erlotinib vs BSC) (95% CI)	Erlotinib	Common reference BSC or V/I	Main comparator	Treatment effect (main comparator vs BSC) (95% CI)	Indirect estimate of effect (erlotinib vs main comparator) (95% CI)
12-month survival rate (erlotinib vs docetaxel), n/N %						
BR.21	RR: 1.49 (1.13, 1.98)	150/488 (30.7%)	**BSC** 50/243 (20.6%)			Relative ratio of RR: 0.50 (0.21, 1.20)
Shepherd (2000)			**BSC75** 6/49 (12.2%)	**D75** 20/55 (36.4%)	RR: 2.97 (1.30, 6.79)	
Fossella (2000)			**V/I** 25/123 (20%)	**D75** 42/125 (34%)	NR	NR
Median (95% CI) overall survival in months (erlotinib vs gefitinib)						
BR.21	HR: 0.73 (0.60, 0.87)	6.7 (5.5, 7.8)	**BSC** 4.7 (4.1, 6.3)			NR
ISEL			**BSC** 5.1 (NC)	**Gefitinib** 5.6 (NC)	HR: 0.89 (0.78, 1.03)	

CI = confidence interval, BSC75 = best supportive care 75mg/m^2, D75 = docetaxel 75mg/m^2, V/I = vinorelbine/ifosfamide, RR = relative rate, HR = hazard ratio, NR = not reported, NC = not calculated

Post hoc analysis of data from the key Trial BR.21 suggested that erlotinib produced a longer duration of survival in patients who were EGFR-positive; no survival benefit was seen in EGFR-negative patients. However, the mutational status was unknown for a significant proportion of the trial population; the trial confidence intervals for the sub-groups were wide and overlapping; only 52% (11/21) of responders had the activating gene; and a test for interaction based on the Trial BR.21 results showed that EFGR status was not associated with survival (p value = 0.97). Thus, overall, the evidence presented suggested that a PBS listing of erlotinib on the basis of EFGR status was not required.

The clinical safety profile of erlotinib was typical of EGFR inhibitors. The incidence of adverse events with erlotinib was similar to BSC, with the exception of rash and diarrhoea. Unlike docetaxel, there was no evidence of bone-marrow toxicity, neutropenic fever, septic complications or neurosensory toxicity associated with erlotinib. The toxicity profile of erlotinib appeared similar to that of gefitinib.

For PBAC's view of these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that erlotinib had similar effectiveness to docetaxel, but a different toxicity profile which was not associated with the haematological toxicities; and significant advantages in effectiveness over BSC, but having more toxicity. The PBAC noted that the randomised trial data supported the second of these descriptions against BSC. The indirect comparison against docetaxel showed no statistically significant difference between docetaxel and erlotinib, however it favoured docetaxel such that a statistically significant survival advantage for docetaxel could not be excluded.

10. Economic Analysis

The submission presented a cost-effectiveness (vs BSC), a cost-minimisation (vs docetaxel) and a cost-consequence (vs gefitinib) approach for the preliminary economic evaluations. As PBAC had ruled gefitinib out as a comparator, no consideration was given to the cost-consequence analysis.

In the preliminary economic evaluation against BSC, the trial-based incremental cost per extra life-year gained was in the range of $75,000 - $105,000 over BSC. Using differences in medians with 95% CI: the incremental cost per extra life-year gained was in the range of $75,000 - $105,000 to > $200,000, thus reflecting a considerable uncertainty around the incremental cost effectiveness ratio (ICER).

A modelled economic evaluation was presented. The base case modelled incremental discounted cost per extra discounted life-years gained was in the range of $45,000 - $75,000.

The PBAC did not consider the cost-minimisation analysis against docetaxel to be appropriate.

For further information on PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The net cost to the PBS was estimated to be < $10 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC recalled that response to gefitinib correlates to presence of the activating mutation (or mutations) of the epidermal growth factor receptor (EGFR) gene in tumour material, whereas response to erlotinib also correlates to expression of the EGFR gene (without mutation) and EGFR gene copy number. Any targeting of erlotinib would need to take all three of these factors into account. The PBAC noted that the submission postulated that erlotinib was effective against wild-type EGFR because of the ability to achieve a higher plasma AUC with erlotinib than gefitinib, which was not active against wild-type EGFR, but the PBAC considered this argument to be weak.

Further, post hoc analysis of data from the key Trial BR.21 suggested that erlotinib produced a longer duration of survival in patients who were EGFR-positive; no survival benefit was seen in EGFR-negative patients, although the analyses were not conclusive because of wide and overlapping confidence intervals. However, it was also noted that the mutational status was unknown for a wide proportion of the trial population; the trial confidence intervals for the sub-groups were wide and overlapping; only 52% (11/21) of responders had the activating gene; and a test for interaction based on the Trial BR.21 results showed that EFGR status was not associated with survival (p value = 0.97). Thus, overall, the evidence presented suggested that a PBS listing of erlotinib on the basis of EFGR status was not required.

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 comparisons of erlotinib versus docetaxel, erlotinib showed numerically similar effectiveness to docetaxel. The PBAC noted that the submission claimed that erlotinib was described as having similar

effectiveness to docetaxel, but a different toxicity profile which was not associated with the haematological toxicities; and significant advantages in effectiveness over BSC, but having more toxicity. Randomised trial data supported the second of these descriptions against BSC. The indirect comparison against docetaxel showed no statistically significant difference between docetaxel and erlotinib, however it favoured docetaxel such that a statistically significant survival advantage for docetaxel cannot be excluded.

The PBAC considered that the cost-minimisation analysis of erlotinib with docetaxel was inappropriate as both costs and effectiveness need to be taken into consideration in assessing the cost-effectiveness of erlotinib.

In the preliminary economic evaluation against BSC, the trial-based incremental cost per extra life-year gained was in the range of $75,000 to $105,000 over BSC. Using differences in medians with 95% CI: the incremental cost per extra life-year gained was in the range $75,000 - $105,000 to > $200,000, thus reflecting a considerable uncertainty around the incremental cost effectiveness ratio (ICER). However, the base case modelled incremental discounted cost per extra discounted life-years gained was in the range of $45,000 - $75,000. The 95% CI of survival extrapolation, which did not reflect the uncertainty over the estimate of the hazard ratio, were also in the range $45,000 - $75,000. The PBAC also noted that the modelled ICER was sensitive to the time horizon and health care resources. These cost-effectiveness ratios were considered high and uncertain and would be even higher if quality adjusted.

The PBAC therefore rejected the submission because equi-effectiveness with docetaxel had not been demonstrated and uncertain cost-effectiveness in comparison with BSC. The PBAC considered that any re-submission should also present a comparison with 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 is planning to resubmit an application for PBS listing for erlotinib.