7.3 ERLOTINIB, 25 mg tablet, 30, 100 mg tablet, 30 and 150 mg tablet, 30, Tarceva®, Roche Products Pty Limited.

1 Purpose of application

1.1 The current last-line PBS restriction for erlotinib is for patients with non-small cell lung cancer (NSCLC) who are not selected on the basis of epidermal growth factor receptor (EGFR) mutation testing.

1.2 The PBAC requested that the sponsor make a submission to establish the effectiveness and cost effectiveness of erlotinib in the population defined by this restriction.

2 Requested listing

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer
ERLOTINIB Tablet 25 mg (as hydrochloride)	30	3	Tarceva Roche
ERLOTINIB Tablet 100 mg (as hydrochloride)	30	3	Tarceva Roche
ERLOTINIB Tablet 150 mg (as hydrochloride)	30	3	Tarceva Roche

2.1 Initial treatment:

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Treatment Phase:	Initial treatment
Restriction:	Section 85 - Authority Required
Treatment criteria:	The patient must be undergoing monotherapy for the condition; AND The patient must have previously been treated with platinum-based chemotherapy
Clinical criteria:	~~The condition must be non-squamous, OR~~ ~~The condition must be not otherwise specified (NOS);~~ ~~AND~~ The patient must have a WHO performance status of 3 or less AND The condition must have progressed following treatment with docetaxel or pemetrexed, OR The patient must have a contraindication or intolerance to treatment with treatment with docetaxel and pemetrexed AND The patient must not be able to receive further chemotherapy subsidised by the PBS or from other sources following treatment with erlotinib
Population criteria:	The patient must have a wild type epidermal growth factor receptor (EGFR) gene; OR The patient must have an epidermal growth factor receptor (EGFR) gene of unknown type.
Prescriber Instructions:	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Non-Small Cell Lung Cancer erlotinib Authority Application Supporting Information Form, which includes: i. Evidence that the patient has been treated with platinum-based chemotherapy AND

	ii. Evidence that disease progression has occurred following treatment with docetaxel or pemetrexed. In patients in whom docetaxel or pemetrexed is contraindicated or cannot be tolerated the prescriber must state the reasons for intolerance or the contraindication; iii. A declaration from the prescriber that the patient has exhausted all opportunities for treatment with chemotherapy either on the PBS, through special access schemes or in a clinical trial. (3) a signed patient acknowledgement.

2.2 Continuing treatment:

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Treatment Phase:	Continuing treatment
Restriction:	Section 85 - Authority Required
Treatment criteria:	The patient must be undergoing monotherapy for the condition; AND The patient must have previously been issued with an authority prescription for erlotinib.
Clinical criteria:	The patient must not have progressive disease.
Population criteria:	The patient must have a wild type epidermal growth factor receptor (EGFR) gene; OR The patient must have an epidermal growth factor receptor (EGFR) gene of unknown type.
Prescriber Instructions:	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Non-Small Cell Lung Cancer erlotinib Authority Application Supporting Information Form, which includes: i. Evidence that the patient has been treated with platinum-based chemotherapy AND ii. Evidence that disease progression has occurred following treatment with docetaxel or pemetrexed. In patients in whom docetaxel or pemetrexed is contraindicated or cannot be tolerated the prescriber must state the reasons for intolerance or the contraindication; iii. A declaration from the prescriber that the patient has exhausted all opportunities for treatment with chemotherapy either on the PBS, through special access schemes or in a clinical trial. (3) a signed patient acknowledgement.

2.3 The submission proposes some changes to the wording of the Section 85 Authority Required listing for the last-line erlotinib treatment of EGFR wild-type or unknown locally advanced or metastatic NSCLC as implemented following the PBAC recommendation made out-of-session between the July and November PBAC 2013 meetings.

3 Background

3.1 Erlotinib was registered by the TGA for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy.

3.2 Erlotinib has been considered by the PBAC for this indication on six occasions, four between March 2006 and March 2008, and twice in 2013: at the July 2013 PBAC meeting and the subsequent out-of-session consideration.

3.3 Erlotinib was first recommended by the March 2008 PBAC meeting for PBS listing as second-line therapy without reference to EGFR mutation status.

3.4 The July 2013 PBAC meeting deferred a decision in relation to the first-line use of erlotinib in EGFR-positive patients, but foreshadowed its intention to replace the existing erlotinib restriction with one which limits eligibility to erlotinib to those patients with an EGFR mutation, but which makes no reference to any line of therapy.

3.5 The subsequent out-of-session consideration by PBAC recommended adding the foreshadowed erlotinib restriction which limits eligibility to erlotinib to those patients with an EGFR mutation without reference to any line of therapy. It also recommended tightening the existing restriction without reference to EGFR mutation status from second-line to last-line (i.e. those patients who have exhausted all opportunities for treatment with chemotherapy), whilst requiring a major submission to be presented to assess the effectiveness and cost effectiveness of erlotinib in the last-line setting for patients with wild-type of unknown EGFR status as an alternative to best supportive care (BSC).

4 Clinical place for the proposed therapy

4.1 65% of patients with NSCLC have advanced stage disease at the time of diagnosis. Patients with non-squamous or not otherwise specified (NOS) NSCLC are eligible for MBS-funded tests to determine EGFR mutation status. About 15% of these patients exhibit mutations of the EGFR, and are eligible for a TKI.

4.2 Patients with squamous NSCLC (approximately 35% of NSCLC patients) are not tested for EGFR mutation status because activating EGFR mutations are very rare in this histology subgroup. NSCLC patients with squamous histology generally have more aggressive disease, with rapid deterioration of performance status and poor survival and have fewer treatment options.

4.3 The submission proposed that, as last-line therapy, erlotinib is intended to be retained for patients who have exhausted all chemotherapy options. This patient group essentially comprises untested patients with squamous NSCLC (who would predominantly be EGFR wild type) and tested patients with non-squamous/NOS NSCLC (who would be EGFR wild type because patients with EGFR mutations would have already been treated with a TKI). The request was considered in the context of the PBAC's recent recommendation to align the current restrictions for tyrosine kinase inhibitors (TKIs), including a requirement for an EGFR mutation and no specification of any line of therapy.

5 Comparator

5.1 The submission nominated best supportive care (BSC) as the comparator. The PBAC considered this to be appropriate.

6 PBAC consideration of the evidence

Consumer comments and sponsor hearing

6.1 The PBAC noted the input from three health care professionals and one organisation via the Consumer Comments facility on the PBS website. Most comments described a range of benefits of retaining the last-line listing of erlotinib including prolonging disease stabilisation and overall survival and maintaining quality of life. The PBAC particularly noted a letter from the Medical Oncologists Group of Australia (MOGA),

which indicated that its PBAC Medical Oncology Advisory Committee would not recommend the use of erlotinib in patients with EGFR-wild-type NSCLC, and would instead support the use of appropriate effective targeted therapies for specific subsets of patients with NSCLC, and cancer in general.

6.2 There was no hearing for this item.

Clinical trials

6.3 The submission relies on the BR.21 trial and associated subgroup analyses.

Trial ID	Protocol title/ Publication title	Publication citation

BR.21	• Protocol 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. Research Report BR.21/June 15, 2004.
	• Main publication: Shepherd FA *et al*. Erlotinib in previously treated non-small-cell lung cancer.
	• Publication of subgroup analyses:
	  • Tsao M-S *et al.* Erlotinib in lung cancer - molecular and clinical predictors of outcome.
	  • Zhu CQ *et al.* Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21.
	• Two further unpublished subgroup analyses.
		N Engl J Med 2005; 353: 123-32
		
		N Engl J Med 2005; 353: 133-44
		J Clin Oncol 2008; 26: 4268-75.

Source: Table B.2.3, p8 of Section B of the submission.

6.4 The PBAC agreed that the relevant population for use of erlotinib (i.e. after all chemotherapy options are exhausted) is essentially those with EGFR wild type tumours (whether tested non-squamous or not otherwise specified NSCLC or untested squamous NSCLC). This is the consequence of the previous erlotinib PBS restriction for later line therapy of advanced NSCLC without reference to EGFR mutation status being overtaken by more recent PBS restrictions for an episode of TKI therapy of EGFR mutation-positive advanced NSCLC without reference to any line of therapy.

6.5 The PBAC therefore agreed with ESC that the participants in the BR.21 randomised trial do not represent patients managed in modern day clinical practice. In particular, this trial was undertaken in an era where EGFR (and ALK) status was not known, and NSCLC was classified differently. Further, despite the assurances conveyed from the trial's principal investigator by the pre-subcommittee response (PSCR), the trial participants do not meet the PBS restriction of having exhausted all chemotherapy options and are therefore only suitable for BSC. This is because [redacted]% of trial participants received subsequent anticancer therapy comprising chemotherapy, EGFR inhibitors and/or radiation therapy. [redacted]% of patients had only one prior chemotherapy regimen. The PBAC noted the more detailed description of the trial population provided in the pre-PBAC response did not change this conclusion.

6.6 The PBAC considered that any concern regarding the representativeness of the broader BR.21 sample to the relevant PBS population (exhausting all chemotherapy

options) applies equally to any of these subgroup analyses drawn from BR.21, published or otherwise. The two published retrospective exploratory subgroup analyses according to EGFR status were interpreted with caution; for example less than 30% of the ITT population had a biopsy sample suitable for later EGFR testing.

6.7 The PSCR presented baseline data by treatment arm for both unpublished subgroups. There were no large imbalances across arms for the parameters reported, but the possibility of residual confounding could not be excluded. The PBAC considered that the relevance of the EGFR wild type or "unknown" unpublished subgroup (comprising 93% of the ITT population) is limited because of the large proportion of "unknown" patients who were not subsequently tested for EGFR mutations (primarily due to lack of sample availability). These untested patients would include patients with EGFR mutations. In Australian clinical practice, however, untested patients would primarily have squamous disease; >99% of whom would have EGFR wild type disease. The PBAC therefore considered that these patients are not "unknown" as such. Of the two populations, the squamous histology unpublished subgroup (comprising 30% of the ITT population) was therefore potentially more relevant for further analysis.

Comparative effectiveness

The progression-free survival and overall survival results from the BR.21 trial for the intention-to-treat population [redacted] are summarised in the table below.

Variable	ITT		EGFR wild type or unknown subgroup		Squamous subgroup	
	Erlotinib	BSC	Erlotinib	BSC	Erlotinib	BSC
OS (months)	(n=488)	(n=243)	[redacted]			
Median	6.7	4.7				
Difference	2.0					
Truncated mean						
Difference			1.4		2.0	
HR (95% CI)	0.73 (0.60, 0.87)					
PFS (months)	(n=488)	(n=243)				
Median	2.2	1.8				
Difference	0.4					
Truncated mean						
Difference						
HR (95% CI)	0.61 (0.51, 0.73)					

Tests for interaction between treatment effect and subgroups: all p > 0.05
BSC=best supportive care; HR=hazard ratio; OS=overall survival; PFS=progression free survival

6.8 Quality of life data from the BR.21 trial are limited, see table below.

Variable	Erlotinib (N=488)	BSC (N=243)
Time to symptom deterioration of cough		
Median (weeks)		
Difference (weeks)		
Hazard ratio (95% CI)		
Time to symptom deterioration of dyspnoea		
Median (weeks)		
Difference (weeks)		
Hazard ratio (95% CI)		
Time to deterioration of pain		
Median (weeks)		

Difference (weeks)	[redacted]
Hazard ratio (95% CI)	[redacted]

6.9 The PBAC considered that the extent of benefit of erlotinib over BSC in BR.21, with a median PFS gain of 0.4 months, truncated mean PFS gain of [redacted] months, and overall survival gain of up to 2 months, was small. The results for time to symptom deterioration did not support a clear conclusion of improved quality of life of erlotinib over BSC. The PBAC further considered that these results represent a best case scenario because patients with EGFR mutation positive tumours (who would be excluded by the current last-line PBS restriction) cannot be excluded from these results and their retention tends to overestimate the effectiveness of erlotinib compared to its use in contemporary patients who meet the current last-line PBS restriction.

Comparative harms

6.10 Safety data from the BR.21 trial were available for patients who received at least one dose of study treatment, see table summarising the incidence of adverse events (AEs) below.

Adverse event	**Erlotinib (N=485) n (%)**	**BSC (N=242) n (%)**	**Relative risk (95% CI) Erlotinib vs BSC**
Patients with ≥1 AE	[redacted]	[redacted]	[redacted]
Patients with ≥1 treatment-related AE	[redacted]	[redacted]	[redacted]
AEs regardless of causality by severity			
NCI-CTC grade 1	[redacted]	[redacted]	[redacted]
NCI-CTC grade 2	[redacted]	[redacted]	[redacted]
NCI-CTC grade 3	[redacted]	[redacted]	[redacted]
NCI-CTC grade 4	[redacted]	[redacted]	[redacted]
Treatment-related AEs by severity			
NCI-CTC grade 1	[redacted]	[redacted]	[redacted]
NCI-CTC grade 2	[redacted]	[redacted]	[redacted]
NCI-CTC grade 3	[redacted]	[redacted]	[redacted]
NCI-CTC grade 4	[redacted]	[redacted]	[redacted]
Patients with ≥1 serious AE	[redacted]	[redacted]	[redacted]
Patients with at ≥1 treatment-related serious AE	[redacted]	[redacted]	[redacted]
Patients who discontinued study due to treatment-related AEs	[redacted]	[redacted]	[redacted]
Patients who died within 30 days of last treatment dose	[redacted]	[redacted]	[redacted]
Patients who died due to a treatment-related AE	[redacted]	[redacted]	[redacted]

Statistically significant differences between the treatment arms are **bolded**
BSC = Best supportive care; AE = adverse event, CI = confidence interval, NCI-CTC = National Cancer Institute Common Toxicity Criteria

6.11 Overall, the majority of AEs were more frequent in the erlotinib arm compared to the BSC arm and were consistent with the known toxicity profile of erlotinib. The incidences of any grade AEs, which were more frequent (>5% difference) in the erlotinib arm than in the placebo arm, are summarised below:

- skin and subcutaneous tissue disorders: [redacted] vs [redacted] (rash: [redacted] vs [redacted]);
- gastrointestinal disorders: [redacted] vs [redacted];
- metabolism and nutrition disorders: [redacted] vs [redacted];
- infections and infestations: [redacted] vs [redacted]; and
- eye disorders: [redacted] vs [redacted].

6.12 The incidences of Grade 3-4 AEs were higher in the erlotinib arm vs the BSC arm for rash ([redacted] vs [redacted]) and gastrointestinal disorders ([redacted] vs [redacted]).

6.13 The PBAC noted that these results in relation to elevated harms with erlotinib needed to be considered in the context of the evidence of small benefits and equivocal quality of life gains from small differences in time to NSCLC symptom deterioration.

6.14 In summary, the ITT analysis and various subgroup analyses of BR-21 suggested, at best, an approximate 2-month median OS increment associated with erlotinib over BSC and a less favourable harm profile for erlotinib than BSC.

Clinical claim

6.15 The submission claimed that erlotinib is superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care for the PBS population. The PBAC considered that the inference of superior effectiveness was not well supported by the evidence because the most relevant evidence presented are exploratory, retrospective subgroup analyses. The PBAC further considered that these results represent a best case scenario because patients with EGFR mutation positive tumours (who would be excluded by the current last-line PBS restriction) cannot be excluded from these results and their retention tends to overestimate the effectiveness of erlotinib compared to its use in contemporary patients who meet the current last-line PBS restriction.

6.16 For the unpublished squamous histology subgroup from the BR.21 trial, there are limitations regarding the post hoc nature of the subgroup analysis and associated potential for confounding. There are also applicability concerns regarding whether these patients have exhausted available active therapies, despite the assurances conveyed from the principal investigator by the PSCR; particularly as there are data from the BR.21 trial indicating post-trial chemotherapy administration.

6.17 There are additional concerns for the 'ITT' and the unpublished 'EGFR wild type or unknown' populations as being not directly applicable to the intended PBS population because these populations include patients with EGFR mutations.

6.18 For the published post hoc analyses of the EGFR wild-type disease subgroups, (Tsao et al and Zhu et al), the small proportion of the BR.21 ITT population able to be subsequently tested (for EGFR mutation status) also gives rise to additional concerns regarding a high risk for selection bias and confounding.

6.19 In seeking to apply the evidence presented to patients meeting the current last-line PBS restriction, the PBAC advised that it was difficult to conclude with confidence that erlotinib's net benefits over best supportive care would exceed its net harms.

Economic analysis

6.20 The submission presents the cost-utility of erlotinib over BSC in three different patient populations, each of which accepts an improved overall survival with erlotinib:

- BR.21 ITT population;
- BR.21 EGFR wild type or unknown; and
- BR.21 squamous patients.

6.21 The PBAC considered that the first two population groups in the model are not representative of the intended PBS population and so considered only the third analysis. The following table summarises the base case and key sensitivity analyses.

Analysis	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Base case			
Using utilities reported for patients receiving 3rd/4th line treatment in Chouaid (2013)*			
No utility benefit for the erlotinib arm in the progression-free health state**			
No utility benefit for erlotinib arm and using the utilities for patients receiving 3rd/4th line treatment reported in Chouaid (2013)			
14% hospitalised/month in the progression-free state (half of the post-progression state)			
0.68 utility and 14% hospitalised/month for progression-free; 0.53 utility for post-progression			
As for previous AND reduce erlotinib price by 95%			

- The PBAC concluded that, even if it were to accept the claimed extent of benefit from the weak clinical evidence presented, the cost-effectiveness of erlotinib in the last-line setting is likely to be reflected by an ICER in the range of $75,000 - $105,000/QALY . This is based on more representative estimates of utilities from Chouaid (2013) and avoids the model double-counting both prolonged time to progression and time before deterioration of symptoms. However, the re-calculated ICER of between $75,000 and $105,000 still does not consider a disutility associated with erlotinib-related adverse events, which did not reflect the committee's conclusion about the less favourable harm profile for erlotinib than BSC. Therefore, the best estimate of the ICER is likely to be even less favourable. In addition, adjusting for the weak basis of the cost offset claim for hospitalisation further increased the ICER to a new respecified base case in the range $75,000 to $105,000/QALY.

Estimated PBS usage & financial implications

6.22 No estimate was provided of the financial implications of not retaining this particular restriction.

7 PBAC outcome

7.1 The PBAC rejected the submission and recommended the deletion of the current last-line PBS restriction of erlotinib because of uncertain net clinical benefit and unacceptable cost-effectiveness.

7.2 The PBAC recalled that it had requested the submission in order to decide whether the evidence available supported the tighter last-line PBS restriction implemented following its out-of-session recommendation in late 2013 to list erlotinib in the PBS for

patients with advanced NSCLC and an EGFR mutation without defining in which line of therapy it should be used. The PBAC accepted that the appropriate comparator was best supportive care (BSC) in the tighter last-line restriction.

7.3 The PBAC considered that the primary source of evidence presented (the BR.21 trial and various post hoc subgroup analyses) did not represent patients in modern day clinical practice and tended to overestimate the extent of benefit by failing to adequately exclude patients with EGFR mutation positive tumours. The PBAC considered that the estimated extent of benefit of erlotinib over BSC in BR.21, with a median PFS gain of 0.4 months, truncated mean PFS gain of [redacted] months, and overall survival gain of up to 2 months, was small. The results for time to symptom deterioration did not support a clear conclusion of improved quality of life of erlotinib over BSC. By comparison, the safety data from BR.21 demonstrated substantially more patients experiencing adverse events following erlotinib than best supportive care, particularly for treatment-related adverse events, consistent with the known toxicity profile of erlotinib.

7.4 The PBAC considered that, even were it to accept the claimed extent of benefit from the clinical evidence presented, the most likely ICER at the current erlotinib price (at greater than $90,000/QALY) was unacceptably high.

7.5 The PBAC did not consider that it was appropriate to retain a listing on the PBS of a targeted therapy for a population in which the target is absent. In reaching this conclusion, the PBAC noted that it was difficult to conclude with confidence that erlotinib's net benefits over best supportive care would exceed its net harms in the population identified by the current last-line restriction.

Outcome:
Rejected

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.

Sponsor's Comment
Testing for EGFR mutation status was not standard practice at the time the BR.21 trial was performed. Therefore, the clinical efficacy results for the EGFR wild-type/unknown and squamous subgroups are based on exploratory analyses. However, the clinical benefit of erlotinib in the EGFR WT/Unknown and squamous subgroups was consistent with the ITT population of BR.21, and was not statistically significantly driven by EGFR mutation status, as previously accepted by the PBAC. Given that erlotinib is widely prescribed in the last-line setting, it would be unethical to generate additional, prospective, randomised clinical evidence such as the BR.21 trial.

Roche disagrees with the assumptions used in the economic model compiled during the evaluation.

Therefore, Roche is disappointed with the PBAC decision to remove the current last-line restriction for erlotinib from the PBS where there is a high unmet clinical need for patients who cannot tolerate any further toxic chemotherapy and best supportive care is the only alternative. Roche notes that the TGA and Australian and international treatment

guidelines recommend the use of erlotinib as a last-line treatment for all patients, regardless of EGFR mutation status.