Public Summary Document

Product: Erlotinib, tablets, 25 mg, 100 mg, 150 mg (as hydrochloride), Tarceva®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested extension of the current Authority required listing to include initial and continuing first-line treatment, as monotherapy, of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small cell lung cancer in patients with evidence of activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material, who do not have progressive disease.

2. Background

This was the second consideration by the PBAC of erlotinib seeking to extend the current Authority required PBS listing to include first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer. A corresponding minor re-submission to extend the current Medicare Benefits Schedule (MBS) listing of EGFR gene mutation testing was lodged for Medical Services Advisory Committee (MSAC) consideration.

In July 2012, the PBAC and MSAC considered a co-dependent integrated submission for listing of EGFR testing and erlotinib in the first-line treatment setting of locally advanced or metastatic NSCLC. The PBAC rejected the submission on the grounds of unacceptably high and uncertain cost-effectiveness.

For details of the previous PBAC consideration, refer to the July 2012 erlotinib Public Summary Document (PSD) available at:
http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/erlotinib

3. Registration Status

Erlotinib was TGA registered on 10 July 2012 for the following indication:

- the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.

Erlotinib is also TGA registered for the following indications:

- maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy. Efficacy is influenced by tumour characteristics.
- treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
- Erlotinib in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

4. Listing Requested and PBAC's View

Authority required

Initial PBS-subsidised treatment, as monotherapy, for the first-line treatment of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small cell lung cancer in patients where there is evidence that the patient has an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material.

Authority required

Continuing PBS-subsidised treatment, as monotherapy, of a patient who has previously been issued with an authority prescription for erlotinib and who does not have progressive disease.

The PBAC mostly supported the requested new listing in advising that a restriction for erlotinib should identify initial and continuing treatment, as monotherapy, of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small-cell lung cancer (NSCLC) in patients with evidence that the tumour harbours an activating mutation(s) of the EGFR gene known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs). The restriction should also limit subsidy to persons who have WHO/ECOG performance status 0 to 2 and no evidence of progressive disease.

The PBAC re-affirmed that the definition of the biomarker should not be restricted to the common activating mutations ie L858R at exon 21 and exon 19 deletions, noting that MSAC advised against this, as did the October 2012 EGFR/TKI stakeholder group and the United States guidelines. The PBAC noted the importance of post-marketing surveillance of both EGFR testing and TKI utilisation, and the need for this to be given a priority for appropriate data collection.

The PBAC also re-affirmed that the restriction should not permit PBS subsidy of sequential use of more than one TKI, noting that the EGFR/TKI stakeholder meeting indicated that sequential use was not needed, and the responses from the companies agreed with this. The PBAC noted that some patients may take a "drug holiday", for example to manage side effects. This would result in re-commencement of the same TKI before disease progression, and the PBAC considered that the restriction should not inadvertently deny this possibility.

The re-submission requested that the proposed first-line listing be in addition to the current later-line listing. The PBAC noted that this restriction permits use after failure of platinum-based chemotherapy. The patient's disease must have progressed following treatment with docetaxel or pemetrexed or the patient must have a contraindication or intolerance to docetaxel and pemetrexed, and not be a candidate for further cytotoxic chemotherapy. However, in contrast to the proposed first-line listing, patient eligibility for this current listing does not depend on EGFR status.

The PBAC considered that the evolution of clinical evidence of TKI use in NSCLC no longer supports the retention of a listing which does not restrict use to EGFR mutation positive patients. The PBAC considered that the best available care should be available to patients in the last-line setting, and that this is not the case for erlotinib in EGFR mutation negative patients where there is mounting evidence of net harm. Review and alignment of the current

restriction for TKIs would allow TKIs to be positioned in the treatment algorithm where they would deliver net benefit to EGFR mutation positive NSCLC patients (rather than potential harm because of exposure of patients with EGFR wild type disease to the negative impact of TKIs, particularly in place of effective chemotherapy). For these reasons, the PBAC advised that the proposed erlotinib restriction would need to replace the existing erlotinib restriction such that erlotinib would not be subsidised for EGFR wild type patients. The PBAC also considered that ideally the TKIs should be available for the treatment of EGFR mutation positive NSCLC; for use either as first- or later-line therapy. Accordingly, subsidy of erlotinib in EGFR mutation positive patients would not be limited to any particular line(s) of therapy.

5. Clinical Place for the Proposed Therapy

The re-submission proposed that the clinical place of erlotinib is to replace the most commonly used platinum-based doublet chemotherapy regimens (in particular carboplatin and gemcitabine) as first-line treatment for locally advanced or metastatic non-squamous or NOS advanced NSCLC in patients with evidence of activating EGFR gene mutations. This is as previously accepted by the PBAC.

It was not clear whether Australian physicians will treat patients with a subsequent TKI in this setting following failure of a first-line TKI. The PBAC noted there is no clinical evidence to support the use of erlotinib after prior treatment with another TKI.

6. Comparator

The re-submission nominated two comparators:

1. platinum-based doublet chemotherapy (carboplatin and gemcitabine), and
2. gefitinib (if PBS listed as first-line treatment of EGFR mutation positive advanced NSCLC).

The re-submission acknowledged that afatinib should also be considered as a comparator, but there was inadequate time for the sponsor to include it as a comparator in this re-submission.

The PBAC agreed that these are appropriate comparators

The re-submission also presented evidence in support of the claim that first-line maintenance therapy, after initial chemotherapy and prior to progression, is part of current clinical practice.

Maintenance therapy was included in the comparator arm of the base-case economic model. The PBAC recalled that it rejected the sponsor's proposed inclusion of maintenance therapy in the July 2012 erlotinib submission, and considered that inclusion of maintenance therapy was inappropriate as it represented utilisation of unknown cost effectiveness.

7. Clinical Trials

<u>Comparison with platinum-based chemotherapy</u>

The re-submission presented two open-label randomised trials comparing erlotinib with platinum-based chemotherapy in Stage IIIB or IV NSCLC patients who had not received any prior treatment for their advanced/metastatic disease and who had activating EGFR mutations. The trials presented in the re-submission were the same as those presented in the previous submission; EURTAC (the key trial) in a predominantly Caucasian population, and

OPTIMAL (the supplementary trial) in a predominantly Asian population. The re-submission provided updated results from the final study report for the EURTAC trial (as of the 11 April 2012 data cut-off). EURTAC only included patients with common activating mutations of the EGFR gene (exon 19 deletions and exon 21 L858R point mutations).

Comparison with gefitinib

As in the previous submission, the re-submission presented an indirect comparison between erlotinib (two trials: EURTAC and OPTIMAL) and gefitinib (four studies: IPASS, NEJGSG, Study 0054 and WJTOG3405), using platinum-based doublet chemotherapy as the common reference. The re-submission updated the indirect comparison using the updated results from EURTAC.

Trial data supporting the existing later-line erlotinib listing

The re-submission cited the BR.21 trial as support for retaining the current erlotinib listing. BR.21 was a 2:1 randomised, placebo-controlled, double-blind trial of erlotinib versus best-supportive care (BSC) in 731 patients who had received at least one prior chemotherapy treatment. The primary endpoint was overall survival. Of the total population, tumour responses were validated centrally for the first 333 patients in the trial. The trial was completed in 2004 (database lock following 582 deaths), having been conducted in a context where pemetrexed was not yet available and prior platinum doublet chemotherapy was typically with docetaxel. Approximately 50% of the randomised patients had received only one prior chemotherapy regimen.

EGFR status was not an inclusion criterion (nor a stratification factor) for the study. A post-hoc exploratory analysis examined the correlation between EGFR status and both survival and treatment response. The claim that EGFR status has no effect on survival relied on a test for interaction between the two mutation groups.

The PBAC recalled that, although it had previously considered the BR.21 trial, this was in relation to effectiveness of erlotinib in the third-line setting, rather than an acceptance of the sponsor's conclusions with respect to the EGFR mutation positive and wild-type sub-groups. The PBAC considered that patients currently receiving PBS-subsidised erlotinib are not mainly doing so as last-line therapy in place of BSC as the only other option and so do not reflect the circumstances of the last-line patients enrolled in the BR.21 study. The PBAC also agreed that this study of non-selected patients would be even less relevant if, as a result of the co-dependent consideration by MSAC, EGFR mutation testing were subsidised for all patients with NSCLC, because then there would be no cost deterrent to knowing the EGFR status of all these patient. Most patients with NSCLC would thus be known to have an EGFR mutation or to have wild-type status, so PBAC considered that requesting that the committee retain the non-selective later-line restriction for erlotinib in that context would amount to requesting that it endorse the use of erlotinib in wild-type NSCLC.

In this regard, the PBAC also noted that subsequent studies have assessed erlotinib in patients known to have EGFR wild-type NSCLC (eg TAILOR study, ASCO 2012; DELTA study ASCO 2013). Further, the PBAC considered that the wider body of evidence for TKIs is also relevant, including the TORCH, TITAN, EURTAC, OPTIMAL, INTEREST and IPASS studies and their sub-group analyses as relevant. Another relevant study, FASTACT-2, had just been published in the July 2013 issue of Lancet Oncology.

For details of published trials and associated reports from EURTAC and OPTIMAL, refer to the erlotinib July 2012 Public Summary Document (PSD).

8. Results of Trials

Comparison with platinum-based chemotherapy

The PBAC recalled from its July 2012 consideration of erlotinib that the key EURTAC trial in mutation positive patients suggested a statistically significant and potentially clinically important benefit for erlotinib monotherapy over platinum-based chemotherapy. An additional median progression-free survival of approximately 4.5 months (26 January 2011 cut-off) compared to platinum chemotherapy was observed. Analysis of EURTAC data at the 11 April 2012 cut-off demonstrated an advantage in progression free survival (PFS) of 5.3 months (HR 0.34 (0.23, 0.49); $p<0.0001$) of erlotinib over platinum-based chemotherapy.

The PBAC reiterated that the key EURTAC trial in mutation positive patients convincingly demonstrated both a statistically significant and clinically important benefit for erlotinib monotherapy over platinum-based chemotherapy in terms of an additional median progression-free survival.

The PBAC considered that the clinical benefit of erlotinib in this setting offers an improvement in quality of life, but not a prolongation of life.
The PBAC recalled also that, because the EURTAC trial allowed for cross-over on disease progression, the results for overall survival inform a comparison of early versus late erlotinib; these results currently show no additional overall survival benefit for first-line erlotinib over chemotherapy.

Indirect comparison with gefitinib

The PBAC considered that the re-analysis of the indirect comparison between erlotinib and gefitinib, based on the updated data from the EURTAC trial, did not alter its previous conclusions.

The PBAC considered that it is difficult to conclude whether erlotinib is non-inferior in terms of effectiveness compared to gefitinib or afatinib based on the evidence presented in the submissions due to differences in the doublet chemotherapy regimens, doubts about exchangeability across the trials included in the indirect comparisons and a lack of a clear basis to determine a minimal clinically important difference. Having regard to these issues, the PBAC concluded that, on balance, the three TKIs erlotinib, gefitinib and afatinib are clinically non-inferior to each other. The PBAC recalled that this pragmatic conclusion reflected the consensus view from the October 2012 EGFR/TKI stakeholder meeting, which was that no clinical preference was expressed for one TKI over another.

In these circumstances, the PBAC determined the equi-effective doses as being erlotinib 150 mg daily, gefitinib 250 mg daily and afatinib 40 mg daily on the basis of the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration.

Current non-specified listing

The PBAC reviewed the history of its consideration of the current erlotinib listing and of the BR.21 trial cited in support, noting that the matter had been considered five times between 2006 and 2008, and that the role of EGFR mutation status did not feature after the initial consideration in March 2006.

The PBAC noted that the evaluation advice to the March 2006 PBAC meeting summarised the re-analysis of the BR.21 results by EGFR mutation status in the following way:
'Post hoc analysis of data from key trial BR21 suggests that erlotinib produces a longer duration of survival in patients who are EGFR-positive; no survival benefit was seen in EGFR-negative patients, although the analyses were not conclusive because of wide and overlapping confidence intervals.'

The following three papers published at the time of PBAC consideration in March 2006 also reported on EGFR status and response to erlotinib are shown in the following table:

Authors	***Patients with somatic mutations***	
	Responders	***Non-responders***
Pao et al (2004)	*5/7*	*0/10*
Jänne et al	*3/5*	*0/8*
Tsao et al (2005)	*3/9*	*16/91*
Total	*11/21 (52%)*	*16/109 (15%)*

Overall, across the three studies combined, 11 out of 21 responders (52%) demonstrated somatic mutations of the EGFR gene while 16 out of 109 non-responders (14.7%) to erlotinib therapy had such mutations'.

The PBAC also considered the re-analysed data from the BR.21 (by Tsao et al., 2005 NEJM (353), pp133-44) supplied with the submission, which reported that hazard ratio for the wild type sub-group was 0.73 (95% CI, 0.49-1.10) and for the mutation subgroup was 0.77 (95% CI, 0.40-1.50), noting the very small patient numbers as a proportion of the trial population. A test for interaction suggested mutation status had no effect on survival (p=0.97). However, the PBAC also noted the sponsor's submission also commented that the post-hoc analyses were 'underpowered and make no adjustment for multiplicity of inferences'.

The same authors published a further paper (Zhu et al., 2008 J Clin Oncol (26), pp4268-75) in which two new methods were used to re-analyse the BR.21 samples, where tissue was available. 233 samples were considered adequate for mutation analysis – only exons 19 and 21 were sequenced for this study. 169 of the samples were from patients who had been analysed by Tsao et al. The authors observed that, *"…the survival benefit from erlotinib compared with placebo was slightly greater with EGFR mutations (HR=0.55; 95% CI, 0.25-1.19; P=0.12) than EGFR wild-type or indeterminate variants (HR=0.74; 95% CI, 0.52-1.05; P=0.09), but the interaction was not significant (P=0.47)"*. However the PBAC also noted that the authors stated that response rate correlates significantly with EGFR mutations (27% v 7%; P=0.035 in 116 assessable patients with known EGFR status).

The PBAC recalled that it recommended listing on the basis of the intention to treat (ITT) results from the BR.21 study which showed benefit in unselected patients in terms of median

overall survival (erlotinib vs. BSC, 6.6 vs. 4.7 months). The PBAC considered that this listing had been interpreted in clinical practice as an option for EGFR mutation negative patients, and that this was inconsistent with the Committee's intention. The PBAC did not consider that use of erlotinib in EGFR mutation negative patients was supported by clinical evidence, and that use in this subgroup had not been deemed cost effective.

Against this series of post hoc analyses of a single trial, the PBAC noted the growing body of evidence of inferior outcomes for patients with no activating mutation of EGFR who are treated with TKIs, including:

- TORCH – a multicenter randomized phase III trial designed to demonstrate non-inferiority, in terms of overall survival (OS), between first-line erlotinib followed by cisplatin/gemcitabine at progression, and the standard inverse sequence. The study was terminated at first planned interim analysis because of inferior outcome in the erlotinib arm (median PFS 6.4 months vs. 8.9 months in the chemotherapy arm). The authors reported a statistically significant treatment effect interaction with EGFR mutation status (p=0.006).
- DELTA – a phase III study of 300 patients on erlotinib or docetaxel in second- or third-line NSCLC with wild type or mutant EGFR (ASCO 2013, presenter Yoshio Okano, Japanese study). For patients with EGFR wild type, median PFS was 1.3 months on erlotinib vs. 2.9 months on docetaxel; HR=1.45 (95% CI: 1.1, 1.9). No difference in overall survival was detected.
- TAILOR study – a phase III trial comparing erlotinib with docetaxel as the second-line treatment of 218 NSCLC patients with wild-type EGFR. (Garassino et al., 2012 J Clin Oncol 30:480s suppl; abstr LBA7501). Median PFS was 2.4 months on erlotinib vs. 3.4 months on chemotherapy (p=0.014).
- TITAN study – a randomised multicentre, open-label, phase 3 study of erlotinib vs. docetaxel or pemetrexed in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (Ciuleanu et al., 2012 Lancet Oncol (13) pp300-8). TITAN failed to prove superiority of erlotinib, with a trend was towards worse survival in the erlotinib arm (median PFS was 6.3 weeks vs. 8.6 weeks in the chemotherapy arm; HR=1.19; 95% CI: 0.97-1.46, p=0.89).
- IPASS (gefitinib), EURTAC (erlotinib) and OPTIMAL (erlotinib) all reported PFS gain only in the EGFR mutation positive group.

The PBAC concluded with particular reference to TAILOR and DELTA that patients with EGFR wild type NSCLC do significantly worse if treated with erlotinib than if treated with docetaxel chemotherapy. The wider body of evidence supports this conclusion of a negative outcome from erlotinib and other TKIs for these patients.

The PBAC further considered that retaining the non-specific restriction would mean actively endorsing the use of erlotinib in EGFR wild type patients where there is evidence of inferior effectiveness to chemotherapy.

The PBAC noted also that the current listing will become redundant once TKIs become available for first-line therapy, since:

- patients' EGFR status will be determined at point of diagnosis; and
- there are no data to support sequential use of one TKI after the failure of another.

Overall, the PBAC did not consider that the current body of evidence was supportive of the use of erlotinib in EGFR mutation negative patients.

The PBAC therefore agreed that retaining the non-selective second-line listing at the same time as introducing a selective first-line listing would amount to overall net harm for patients with wild-type (mutation-negative) NSCLC. Rather, the PBAC considered that limiting access to TKIs to patients with NSCLC and activating EGFR mutations would position this class of agents in the treatment algorithm where they would deliver a net benefit to patients. The PBAC noted that placing TKIs in first-line for EGFR mutation positive NSCLC would also be consistent with clinical practice guidelines and the consensus of the EGFR/TKI stakeholder meeting.

With regard to the comparative harms, the PBAC noted that the re-submission provides an overall summary of safety data from the EURTAC trial, based on the final analysis (data cut-off 11 April 2012). No new safety issues were identified. As the EURTAC trial was non-blinded, there is considerable potential for observation bias in the reported safety data.

The PBAC agreed that the TKIs have slightly different toxicity profiles (eg afatinib has more diarrhoea) and, although the side effects are manageable, the availability of multiple TKIs would allow greater choice for patients. The PBAC also noted that toxicity is most often managed clinically by dose reduction rather than switching to another TKI.

9. Clinical Claim

The re-submission described erlotinib as superior in terms of comparative effectiveness over platinum-based doublet chemotherapy. The re-submission did not make any claims regarding the comparative safety of erlotinib and platinum-based chemotherapy, only stating that the toxicity profiles of the two treatments differ.

The PBAC considered that these claims were reasonable.

The PBAC noted there is no comparative clinical evidence in patients with rare activating mutations of the EGFR gene. MSAC has noted that the common mutations account for some 70% of the EGFR activating mutations and that a broad biomarker definition, though encouraging broader reporting of mutations, would therefore not be based on strong evidence. The PBAC considered that, noting the consensus of the EGFR/TKI stakeholder meeting, it was reasonable to accept the use of erlotinib in uncommon mutations.

For the comparison with gefitinib, the re-submission described erlotinib as no worse than gefitinib in terms of both comparative effectiveness and comparative safety.

The PBAC agreed that, on balance, erlotinib is likely to be non-inferior compared to gefitinib or afatinib.

10. Economic Analysis

The submission presented:

- A cost utility analysis based on the claim of superior efficacy and differential safety profile of first-line erlotinib versus first-line chemotherapy for patients with common EGFR mutations.
- A cost-minimisation analysis based on a non-inferiority claim for progression-free and overall survival between erlotinib and gefitinib, but not including additional costs/offsets for administration/adverse events.

The model included three lines of treatment. Within each line of treatment, patients begin in the unprogressed health state in which they may remain, move to being progressed for this line of treatment or die. Patients who progress may remain in the progressed health state, move to being unprogressed for the next line of treatment, or die. Within each health state other than death, there are four sub-states, one for each of the first three months and one for after three months.

The submission models an additional survival benefit for first-line erlotinib compared with both sequences of first-line chemotherapy (with different hazard rates (HRs) for taking on second-line treatment). As the EURTAC key trial provided no evidence of superior comparative effectiveness in terms of overall survival (OS), the PBAC considered it inappropriate for the model to assume an overall survival benefit for first-line erlotinib versus first-line chemotherapy, and that the results were biased in favour of first-line erlotinib.

Based on different HRs for taking on second-line treatment for the two chemotherapy arms, the model uses different transition probabilities for progression through the lines of therapy to death. As a result, one chemotherapy sequence has a modelled additional survival benefit compared with the other. The PBAC considered that, again, no evidence was provided to support a survival advantage from more and quicker uptake of second-line erlotinib in patients who are treated with first-line chemotherapy.

The re-submission claimed an ICER of $45,000 - $75,000/QALY (without pemetrexed maintenance) based on re-analysing individual patient data from the EURTAC trial to estimate the transition probabilities among health states over a five-year time horizon and applying utility weights based on Nafees et al (2008).

The model was sensitive to the following variables:
- the estimates of costs in the comparator arm
- the hazard rates (HRs) for progression in the first-line erlotinib arm
- the estimate of the prevalence of common EGFR mutations
- the selection of utility weights.

<u>Costs in the comparator arm</u>
The model assumed high second-line uptake of a TKI following failure of first-line chemotherapy in the comparator arm, with patients receiving a TKI as first or second-line spend equal durations with stable disease. If 100% of patients are assumed to receive a second-line TKI, first-line chemotherapy costs therefore increase. The resulting ICER is approximately $15,000 - $45,000, despite the lack of a QALY gain for first-line erlotinib. Conversely, if TKI uptake approaches zero and a best case conversion of the PFS gain (of 10.4 months) to a survival gain is assumed (and assuming no utility decrement between first- and second-line stable disease), this results in approximately $75,000 - $105,000/QALY.

The model assumed that all patients in the comparator arm who progress to second-line therapy receive erlotinib regardless of EGFR mutation status. The PBAC considered that this was not consistent with the current listing for erlotinib, which restricts use to patients who have exhausted all chemotherapy options (i.e. last-line). Assuming all patients on second-line treatment in the comparator arm will receive erlotinib overestimates the costs of second-line treatment in the comparator arm, favouring first-line erlotinib.

The re-submission applied a discount to the price of first-line erlotinib and a smaller discount to the price of second-line erlotinib. Sensitivity analysis indicates that if first-line erlotinib was the same price as second-line erlotinib, the ICER would be $105,000 - $200,000/QALY, without considering pemetrexed maintenance.

Pemetrexed maintenance is assumed to be used in 40% of patients who remain progression-free after the first-line chemotherapy, leading to a conclusion of dominance for first-line erlotinib over current management. The PBAC considered that the utilisation of pemetrexed for maintenance therapy, while not expressly excluded by its PBS restriction, has not been deemed cost effective. Further, the PBAC noted that pemetrexed is not included in the erlotinib arm of the model, thereby increasing comparator costs. The PBAC therefore considered that its inclusion as a cost offset was not appropriate.

<u>HRs for progression in the first-line erlotinib arm</u>
The model was very sensitive to the progression rate for:

- patients receiving first-line erlotinib,
- patients on first-line treatment after 3 months
- patients on any erlotinib treatment.

The ICER could reach over $75,000 - $105,000/QALY from the base case of $45,000 – $75,000. The hazard rates used in sensitivity analyses correspond to the 95% confidence interval for the relative hazard rate for the number of progression events observed in the EURTAC trial after 3 months. The model assumed a constant hazard within the first three months and another constant hazard after 3 months, which were not evident from the Kaplan-Meier curves for progression-free survival in the EURTAC trial. The model also assumed that the constant hazard from Month 3 continues until Year 5 or until all patients have progressed/died. The submission presented no evidence for this assumption.

<u>Prevalence of common EGFR mutations</u>
When the prevalence of common EGFR mutations is assumed to be 10% (consistent with MSAC advice as the lower bound for a sensitivity analysis), the ICER exceeds $75,000 - $105,000/QALY.

The model assumed that the EURTAC laboratory-developed test represented the evidentiary standard. Using the COBAS test, 15% of patients were assumed to be tested EGFR mutation positive (the same as the prevalence of EGFR positive mutations advised by the MSAC). The PBAC considered the assumption of test performance to be optimistic.

The submission assumed that patients incorrectly identified as mutation positive (false positive patients) have the same treatment outcomes as those being treated with first-line

chemotherapy, despite being incorrectly treated with first-line erlotinib. The PBAC did not consider that this assumption was reasonable.

Utilities

The model was also sensitive to the decrement between the first-line unprogressed and second-line unprogressed health states. Patients with non-progressing disease on first-line therapy were assumed to be in the stable state, and all other patients (including those stable on second-line therapy) in a post-progressed state. Patients whose disease was stable and who suffered no side effects were assigned a utility of 0.653 directly from Nafees et al (2008), while patients with progressive disease had utilities adjusted from a utility of 0.473 from Nafees et al (2008).

When the utility for the initial unprogressed first-line health state (u1) was decreased to be 0.60, compared with 0.653 at the base case, the ICER increased to $75,000 – $105,000/QALY. When the utilities for the subsequent health states after progression from u1 were increased to be 0.55 for p1/u2, 0.5 for p2/u3 and 0.45 for p3 (compared to the base case values of: 0.5 for p1/u2, 0.45 for p2/u3 and 0.4 for p3), the ICER also increased to$75,000 – $105,000/QALY.

Vignettes from the Nafees et al (2008) study informed the utility weights. The PBAC considered that the use of a vignette-based utility study was inappropriate, and the ensuing utility values were not reliable.

The PBAC noted Economic Sub-Committee (ESC) advice relating to a sensitivity analyses which assumed a utility of 0.653 for both first- and second-line unprogressed health states, the same utilities for the other health states and the disutility associated with chemotherapy treatment using two different representative prices to show the result of a price reduction on cost-effectiveness. Maintenance was not included. The ESC advice calculated two further sensitivity analyses ICERs with these assumptions using two different representative prices to show the result of a price reduction on cost-effectiveness.

The time-horizon of the model is five years. An annual discount rate was applied to both costs and outcomes. This was unchanged from the previous submission.

The PBAC did not accept the claim of dominance of erlotinib, as it was not considered appropriate for costs for pemetrexed maintenance to be applied only in the comparator arm.

The PBAC considered that the more appropriate base case ICER for erlotinib in first-line treatment of NSCLC was $45,000 - $75,000, after excluding the application of pemetrexed maintenance in the comparator arm. The PBAC considered also that this ICER was subject to significant variability, given the sensitivity of the model to EGFR mutation prevalence, method of generating utilities, comparator costs and HRs for disease progression in the erlotinib arm. However, the PBAC also accepted the reality that listing erlotinib as requested would realise cost off-sets to some extent from reduced maintenance with pemetrexed, which would reduce the base case estimate of $45,000 - $75,000/QALY.

The re-submission assumed that erlotinib 150 mg daily is equi-effective to gefitinib 250 mg daily. The duration of treatment for erlotinib was estimated from the EURTAC trial and that for gefitinib was estimated from the IPASS trial. The PBAC considered that, consistent with

its conclusion of non-inferiority between these two drugs, their durations of treatment should not be different.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10, 000 in Year 5, at an estimated net cost per year to the PBS in the range of $10 - $30 million in Year 5.

The PBAC noted discrepancies in the estimated utilisation and net costs to PBS across the submissions for the three TKIs. These arose from differences in:

- the epidemiological basis for estimating the numbers of patients eligible for EGFR mutation testing
- the estimated duration of TKI treatment
- the proposed cost per day for the three TKIs.

12. Recommendation and Reasons

The PBAC advised that a restriction for erlotinib should identify initial and continuing treatment, as monotherapy, of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small-cell lung cancer (NSCLC) in patients with evidence that the tumour harbours an activating mutation(s) of the EGFR gene known to confer sensitivity to treatment with EGFR TKIs. The restriction should also limit subsidy to persons who have WHO/ECOG performance status 0 to 2 and no evidence of progressive disease.

The PBAC welcomed the comments received from individuals via the Consumer Comments facility on the PBS website and noted that these were exclusively from prescribers supporting the retention of the current nonspecific later-line listing for erlotinib. The PBAC noted also the representations of the sponsor on this issue. Overall, the PBAC considered that the evolution of clinical evidence of TKI use in NSCLC no longer supports the retention of this listing. The PBAC considered that the best available care should be available to patients in the last-line setting, and that this is not the case for erlotinib in EGFR mutation negative patients where there is mounting evidence of net harm. For these reasons, the PBAC advised that the proposed erlotinib restriction would need to replace the existing erlotinib restriction such that no line of therapy would be specified for erlotinib in EGFR mutation positive patients.

The PBAC accepted that the comparator for erlotinib and the other two tyrosine kinase inhibitors (TKIs) considered at the same meeting is platinum-based doublet chemotherapy. The type of doublet varied across the three submissions considered, and the PBAC noted that there were likely to be some differences in efficacy of different doublets (e.g. doublets involving pemetrexed are more effective than those involving gemcitabine or paclitaxel in non-squamous NSCLC). However, the PBAC accepted, on balance and for the purposes of the three submissions, that these doublets are clinically non-inferior to each other.

The PBAC accepted that erlotinib and the other two TKIs are more effective than platinum-based doublet chemotherapy in patients with EGFR mutation positive NSCLC in terms of

improving progression free survival (PFS), with the additional gain in median PFS varying between 1.7 and 5.4 months across the key randomised trials presented.

The PBAC noted that there was no significant survival advantage reported for erlotinib or the other two TKIs in these trials. Although the survival analysis in each of the trials was confounded by cross over from doublet chemotherapy to a TKI, given the large number of trial participants who received a second-line TKI, the data suggest that TKIs should be available either as first-line treatment or following doublet chemotherapy. In other words, there is no difference to progression-free survival or overall survival whether a TKI is given as first-line or second-line therapy to patients with EGFR mutation positive NSCLC.

The PBAC noted that the three TKIs have slightly different toxicity profiles. Although the side effects are manageable overall, the PBAC considered that the PBS listing of more than one TKI would allow greater choice for patients.

With reference to indirect comparisons involving different doublet chemotherapies as the common reference, the PBAC noted that there were differences in the doublet chemotherapy regimens, doubts about exchangeability across the trials and a lack of a clear basis to determine a minimal clinically important difference. Having regard to these issues, the PBAC concluded that, on balance, the three TKIs afatinib, erlotinib and gefitinib are clinically non-inferior to each other, and so should be cost-minimised against each other with the equi-effective doses being afatinib 40 mg daily, erlotinib 150 mg daily and gefitinib 250 mg daily (ie as per the key trials). In these circumstances, the PBAC determined the equi-effective doses of afatinib, erlotinib and gefitinib on the basis of the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration.

As for the other two TKIs considered by the PBAC, the economic evaluation for erlotinib compared:

- proposed management of first-line EGFR testing followed by a TKI for mutation positive patients and by doublet chemotherapy for mutation negative patients with
- current management (the comparator) of treatment with cisplatin and gemcitabine chemotherapy without first-line EGFR testing.

The modelled cost-utility analysis of erlotinib lacked transparency. The structure and inputs of the models differed across the three TKI submissions, which contributed to the differences in their outputs and ICERs.

The PBAC rejected the submission's base case of dominance (including maintenance treatment with pemetrexed before disease progression), and instead relied on the base case ICER of $45,000 - $75,000 /QALY (excluding maintenance treatment with pemetrexed before progression, but accounting for false positive EGFR test results). The PBAC recalled that it had expressed concerns in July 2012 with the inclusion of costs for maintenance with pemetrexed before disease progression as being of doubtful cost-effectiveness, and noted that the submission's preferred model assumed that all comparator patients will receive this maintenance without including any additional benefit for this additional cost. However, the PBAC also accepted the reality that listing erlotinib as requested would realise cost off-sets to

some extent from reduced maintenance with pemetrexed, which would reduce the base case estimate of $45,000 - $75,000 /QALY.

A significant limitation of the erlotinib model is its failure to account for any variation in the base case prevalence of 15% for tested patients being EGFR mutation positive. The PBAC noted that, in one sensitivity analysis, if the prevalence of EGFR positive mutations is reduced to the lower limit of 10% advised by MSAC, the ICER increased to beyond $100,000. Similarly, in another sensitivity analysis, which attempted to account for a reduced net benefit in patients with a false positive test result, the ICER increased to beyond $45,000 - $75,000. The PBAC noted that while these ICERs are closer estimates of the ICER for the entire NSCLC population which is tested, they underestimate the per patient clinical benefit to the EGFR mutation positive cohort which is treated.

Further, the PBAC noted a series of other concerns with the model, namely that:

- the model was very sensitive to HRs for progression in the first-line erlotinib arm, with the ICER varying to over $100,000/QALY in sensitivity analysis
- the use of vignettes to generate the model's utilities was not appropriate as more robust estimates would have been obtained from the trial
- the assumption of a difference in utility between first- and second-line unprogressed states was not supported by the evidence and led to an unjustifiable decrease in the ICER.

Overall, the PBAC considered that the base case ICER of $45,000 - $75,000 /QALY was unacceptably high and uncertain.

The PBAC noted discrepancies in the estimated utilisation patterns and net cost to the PBS across the three submissions. The PBAC agreed with advice received during the evaluation that the number of patients with NSCLC who test positive for an EGFR is less than 10,000 in Year 5. The PBAC noted that the costs to the PBS were higher than would be the case if reduced prices were offered and accepted.

The PBAC noted that the biggest financial risk is the duration of therapy, particularly due to use beyond disease progression, which could double the estimate of net costs, and advised that a risk-share arrangement should be negotiated to manage this risk in particular. The negotiated risk-share arrangement should also satisfactorily address the uncertain effectiveness of erlotinib in the 30% of patients expected to have rare EGFR activating mutations, whilst accepting its effectiveness in the 70% of patients expected to have common EGFR activating mutations.

The PBAC deferred the re-submission in order to ascertain whether the applicant is prepared to offer a reduced price for all use of erlotinib under the proposed restriction to patients with NSCLC who are EGFR mutation positive as indicated by the PBAC, and if so, to consider the implications of this reduced price for revising the cost-effectiveness of listing erlotinib.

The PBAC noted that it wished to consider this revised cost-effectiveness in the context of its objective of ensuring better use of all TKIs, including by reducing use of TKIs as currently listed which is not safe or cost-effective . This proposal for the applicant to consider arises from PBAC's broader assessment across the three TKIs resulting in its conclusion of non-inferiority and the resulting equi-effective doses. It is a simple pricing proposal and does not

include a weighted price across use in the first-line treatment and subsequent lines of treatment because there is no discernible difference in clinical outcomes across these circumstances.

The PBAC considered that a major re-submission would be required if the applicant wished to seek a higher price and/or a restriction in which a broader population would be eligible and/or not be prepared to negotiate a risk-share arrangement which satisfactorily addresses risks of excessive utilisation and use in rare EGFR activating mutations as well as forming the basis for price.

The PBAC foreshadowed the following restrictions should the additional information requested through the deferral be sufficient to support a subsequent recommendation to list erlotinib on the PBS.

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

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC)
Phase of treatment:	Initial treatment
Restriction:	Authority required
Treatment criteria:	The patient must be undergoing monotherapy for the condition.
Clinical criteria:	The condition must be non-squamous, **OR** The condition must be not otherwise specified (NOS); **AND** The patient must not have received previous PBS-subsidised treatment with any EGFR tyrosine kinase inhibitor (TKI), **OR** The patient must have developed intolerance to another TKI of a severity necessitating permanent withdrawal of treatment; **AND** The patient must have a WHO/ECOG performance status of 0-2.
Population criteria:	The patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR TKIs in tumour material.

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

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Phase of treatment:	Continuing treatment
Restriction:	Authority required
Treatment criteria:	The patient must be undergoing monotherapy for the condition; **AND** The patient must previously have been issued with an authority prescription for erlotinib.
Clinical criteria:	The patient must not have progressive disease.

Outcome:
Defer

Subsequent to the meeting, the sponsor offered to reduce its price for all use of erlotinib under the proposed restriction to patients with NSCLC who are EGFR mutation positive.

The PBAC therefore recommended out of session the listing of erlotinib on the PBS as an Authority required listing, as monotherapy, for the treatment of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small cell lung cancer in patients with evidence of activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material. Erlotinib is to cease on progression.

The PBAC considered that, at the reduced price, erlotinib could be considered to be cost-effective in comparison with platinum-based doublet chemotherapy, based on erlotinib's superiority in terms of progression free survival and quality of life, and different toxicity profile, despite the evidence showing no additional overall survival benefit for first-line erlotinib over chemotherapy in patients with NSCLC who are EGFR mutation positive.

The PBAC also recommended that a risk-share arrangement be negotiated with the sponsor which satisfactorily addresses risks of excessive utilisation and use in patients with rare EGFR activating mutations. This information regarding usage will inform decisions regarding price.

PBAC re-iterated its previous conclusion that, on balance, erlotinib is likely to be non-inferior compared to gefitinib or afatinib.

The PBAC considered that prioritising the access to TKIs to patients with NSCLC and activating EGFR mutations would position this class of agents in the treatment algorithm where they would deliver a net benefit to patients. The PBAC noted that providing access to TKIs in first-line for EGFR mutation positive NSCLC would also be consistent with clinical practice guidelines and the consensus of the EGFR/TKI stakeholder meeting.

With respect to patients with EGFR wild-type or unknown NSCLC who could be treated with either erlotinib or chemotherapy, the PBAC remained concerned that the weight of evidence indicates that erlotinib is inferior in efficacy to chemotherapy in patients who do not have an EGFRM+ tumour. The PBAC considered that use of erlotinib in place of chemotherapy in patients without EGFR mutations could no longer be supported. Use in this setting would require a new major submission which provided a comprehensive assessment of the clinical and economic data for the use of erlotinib in patients without EGFR mutations who were candidates for chemotherapy.

With respect to patients with EGFR wild-type or unknown NSCLC in the last-line setting who are no longer suitable for chemotherapy and have only BSC as an alternative, the PBAC agreed with the sponsor's request that erlotinib remains available until the effectiveness and cost effectiveness of erlotinib in this setting can be formally reviewed. This will require the sponsor to present a major submission to the March 2014 PBAC meeting 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 BSC.

In the meantime, PBAC recommended the current restriction for the last line listing be amended to specify that there is no option for further treatment with PBS-subsidised chemotherapy following use of erlotinib in the last line setting. To give effect to this recommendation the following changes are requested:

- written Authority required type of listing; and
- the prescriber seeking authority provides evidence that:
    a) the patient has been treated with platinum-based chemotherapy AND
    b) 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;
    c) WHO performance status is 3 or less
    d) the prescriber must provide a declaration that the patient has exhausted all opportunities for treatment with chemotherapy either on the PBS, through special access schemes or in a clinical trial.

Given the changing treatment paradigms for NSCLC and the positive recommendation to list erlotinib for EGFRM+ patients, the PBAC considered that the role of maintenance treatments for NSCLC needs to be reviewed. In particular, the clinical place, effectiveness and cost effectiveness of maintenance treatments used at different stages of disease progression.

Outcome:
Recommend

Last line restriction - initial treatment

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Treatment Phase:	Initial treatment
Restriction:	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 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 a 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.
Administrative Advice	Special Pricing Arrangements apply Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Last line restriction – continuing treatment

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Phase of treatment:	Continuing treatment
Restriction:	Authority required

Treatment criteria:	The patient must be undergoing monotherapy for the condition; **AND** The patient must previously have 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 a epidermal growth factor receptor (EGFR) gene of unknown type
Prescriber Instructions *(Included in LI)*	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: iv. evidence that the patient has been treated with platinum-based chemotherapy AND v. 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; vi. 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.
Administrative Advice	Special Pricing Arrangements apply Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Grandfathering restriction

Severity	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition/Indication:	Non-small-cell lung cancer (NSCLC).
Phase of treatment:	Continuing treatment
Restriction:	Authority required
Treatment criteria:	The patient must be undergoing monotherapy for the condition; **AND** The patient must previously have been issued with an authority prescription for erlotinib prior to *[insert date of amendment of listing]*.
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 a epidermal growth factor receptor (EGFR) gene of unknown type
Administrative Advice	Special Pricing Arrangements apply

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 welcomes the PBAC's decision to recommend the listing of erlotinib for patients with EGFR mutation positive locally advanced or metastatic NSCLC. The Sponsor intends to address the clinical and cost-effectiveness of erlotinib in the last-line setting versus best supportive care for patients with EGFR wild-type or unknown NSCLC, including squamous patients who will not be tested under the proposed MBS restriction, in a resubmission for consideration at the March 2014 PBAC meeting.

The Sponsor however disagrees with the statement regarding mounting evidence of harm in EGFR mutation negative patients in the last-line setting, where best supportive care is the only alternative treatment. The Sponsor contends no clinical evidence supports the statement that there is a net harm associated with erlotinib in this specific patient group. The Sponsor also contends that for patients no longer suitable for chemotherapy, erlotinib remains a safe and effective treatment, regardless of mutation status, as shown in the BR.21 trial. The Sponsor contends this use of erlotinib in the last-line setting is supported by the TGA indication, and Australian and international treatment guidelines.