Public Summary Document

Product: Afatinib, tablets, 20 mg, 30 mg, 40 mg and 50 mg, (as dimaleate) Giotrif®
Sponsor: Boehringer Ingelheim Pty Limited
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought an Authority required listing of afatinib as second/third-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

2. Background

Afatinib had not previously been considered by the PBAC. The PBAC considered that afatinib, like other tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, is co-dependent on epidermal growth factor receptor (EGFR) mutation testing and so found that advice from Medical Services Advisory Committee (MSAC) in relation to EGFR mutation testing in the context of gefitinib or erlotinib is relevant.

3. Registration Status

At the time of consideration in July 2013 the PBAC noted the TGA regulatory application was still pending and that no TGA documents were available.

Afatinib was TGA registered on 7 Nov 2013for the following indication:

as monotherapy for the treatment of patients with advanced or metastatic non-squamous non-small-cell carcinoma of the lung, either as first line therapy or after failure of cytotoxic chemotherapy. Tumours must have epidermal growth factor receptor (EGFR) exon 19 deletions or L858 substitution mutations.

4. Listing Requested and PBAC's View

The submission requested Authority required listing of afatinib as second/third-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients without an EGRF mutation status who have a progressive disease after prior platinum doublet chemotherapy following treatment with docetaxel or pemetrexed; or for whom a further cytotoxic chemotherapy is not tolerated, is contraindicated, or is not appropriate or for whom another TKI other than afatinib is experienced.

The requested listing was based on the claim of non-inferiority by indirect comparisons of second-line treatment of gefitinib and last line treatment of erlotinib.

The PBAC considered the proposed listing was not appropriate because:

- The requested listing restriction is outside the proposed TGA restriction, which requires a positive EGFR mutation status for patients who are receiving afatinib treatment.

- The requested listing restriction includes squamous cell NSCLC, which is inconsistent with the consensus view of the October 2012 tyrosine kinase inhibitors (TKI) stakeholder meeting.
- The requested listing restriction includes TKI (other than afatinib) experienced patients, which has not been justified in the submission.

5. Clinical Place for the Proposed Therapy

The submission proposed that afatinib would substitute for erlotinib in patients with advanced NSCLC, whose EGFR mutation status is unknown or is negative (M-), and for erlotinib and gefitinib in patients who are EGFR M+, and that afatinib would be used following prior treatment with either erlotinib or gefitinib.

The PBAC considered that it is not appropriate for afatinib to be used in a patient with advanced NSCLC whose EGFR mutation status is negative or unknown, as this use is inconsistent with the proposed TGA indication and the consensus view of the October 2012 TKI Stakeholder meeting. The PBAC also considered that there is no evidence to justify use of afatinib following prior treatment with other TKIs in the submission.

6. Comparator

The submission nominated erlotinib and gefitinib as the main comparators. The PBAC considered that it is not appropriate to propose erlotinib as a comparator for afatinib third line therapy as 1) the proposed afatinib TGA indication specifies treatment in patients with EGFR mutation whilst EGFR mutation status is not required in erlotinib third line treatment; 2) the PBAC has signalled that EGFR TKIs should only be used for NSCLC patients with an EGFR mutation positive status during the consideration of the November 2012 gefitinib submission and 3) the consensus view of the October 2012 stakeholder meeting indicated that it would be more appropriate for erlotinib being used for EGFR gene mutation positive NSCLC patients.

The PBAC also considered it is not appropriate to nominate erlotinib or gefitinib as the comparators in the scenario where afatinib was used to treat patients who had been treated with another TKI (erlotinib or gefitinib), as there was no data presented in the submission showing that either erlotinib or gefitinib was used in the same situation. The PBAC considered the appropriate comparator for this listing is likely to be best supportive care.

7. Clinical Trials

The submission presented one randomised trial comparing afatinib 50 mg with placebo in 585 patients with advanced (Stage IIIb / IV) NSCLC who have failed 1-2 lines of cytotoxic chemotherapy and have received prior treatment with erlotinib or gefitinib (LUX Lung 1, which included PFS results from both independent and investigator's assessment). This was indirectly compared to:

- One randomised trial comparing erlotinib 150 mg with placebo in 731 patients with advanced NSCLC who have failed 1-2 lines of cytotoxic chemotherapy (BR.21).

- One randomised trial comparing gefitinib 250 mg with placebo in 1692 patients with advanced NSCLC who have failed 1-2 lines of cytotoxic chemotherapy (ISEL).

The PBAC considered that the evidence presented using the indirect comparisons in this submission is not applicable nor useful for determining the appropriateness of the proposed afatinib listing because the patient population used in clinical trials presented in the submission is not relevant to the requested listing.

The details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
LUX Lung 1		
Miller VA et al.	Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial.	The Lancet Oncology 2012; 13:528-538.
LUX Lung 2		
Yang J et al.	Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial	The Lancet Oncology 2012; 13:539-548.
ISEL		
Thatcher N et al.	Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer).	Lancet 2005; 366:1527-1537
Chang A et al.	Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: Subset analysis from the ISEL study.	Journal of Thoracic Oncology 2006; 1:847-855.
Hirsch FR et al.	Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer.	Journal of Clinical Oncology 2006; 24:5034-5042.
Tyagi P et al.	Updated data from the Iressa survival in lung cancer trial.	Clinical Lung Cancer 2005; 6:340-342.
BR.21		
Shepherd FA et al.	Erlotinib in previously treated non-small-cell lung cancer.	New England Journal of Medicine 2005; 353:123-132
Bezjak A et al.	Symptom improvement in lung cancer patients treated with erlotinib:	Journal of Clinical Oncology 2006; 24:3831-3837.

	Quality of life analysis of the National Cancer Institute of Canada clinical trials group study BR.21.	
Liu G et al.	Pharmacogenetic analysis of BR.21, a placebo-controlled randomized phase III clinical trial of erlotinib in advanced non-small cell lung cancer.	Journal of Thoracic Oncology 2012; 7:316-322.
Tsao MS et al	Erlotinib in lung cancer - molecular and clinical predictors of outcome	The New England Journal of Medicine 2005; 353:133-144.
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.	Journal of Clinical Oncology 2008; 26:4268-4275.

8. Results of Trials

The PBAC considered that the comparative benefits presented in the submission were not relevant to the requested listing as the comparisons were between a post TKI population (LUX lung 1) and a TKI naïve population (ISEL or BR.21).

For the outcome of overall survival the PBAC noted that afatinib was not effective in the post TKI population when compared with placebo (HR [95% CI]: 1.08 [0.86, 1.35] ITT group). The PBAC also noted that afatinib was less effective in the ITT group compared indirectly to the relevant groups of gefitinib (HR [95% CI]: 1.21 [0.93, 1.58]) or erlotinib (HR [95% CI]: 1.54 [1.15, 2.07]).

The PBAC noted that the comparison of progression-free survival (PFS) data of afatinib relative to gefitinib was not available as the ISEL trial reported time to treatment failure rather than PFS.

The PBAC noted that the submission proposed that afatinib was superior to erlotinib for the outcome of PFS (afatinib independent assessment vs erlotinib ITT HR [95% CI]: 0.62 [0.47, 0.83] and afatinib investigator's assessment vs erlotinib ITT HR [95% CI]: 0.61 [0.46, 0.79]). The PBAC considered the estimate may not be valid as the results were derived from indirect comparisons from the two different patient populations (post TKI vs TKI naïve patient).

The submission described the adverse event profiles for the three EGFR TKIs as generally similar, but acknowledged that there may be some differences.

With regard to comparative harms, the PBAC noted that diarrhoea including 'greater than grade 3', rash greater than grade 3, stomatitis and nail effect (paronychia) appeared to be more common in patients receiving afatinib than those receiving erlotinib or gefitinib.

The PBAC noted that dose reductions were more common in the afatinib arm (38.5%) compared with patients receiving erlotinib (19%) and discontinuations due to adverse events

were far higher among patients receiving afatinib (17.9%) than those receiving erlotinib (5%) or gefitinib (5%).

The PBAC noted that afatinib was not registered anywhere in the world and the product safety update reports were not available at the time of the assessment. The submission offered the adverse events in the LUX lung 2 trial as supporting evidence of safety. The rates of adverse events were similar to the LUX lung 1 trial.

9. Clinical Claim

The PBAC noted that the submission stated a pragmatic overall claim that afatinib was non-inferior to erlotinib and gefitinib for the treatment of patients with advanced NSCLC. Consequently, the submission pursued a cost-minimisation approach for establishing pricing for afatinib.

The PBAC considered there were multiple issues with the clinical claim as made in the submission:

- The evidence to support non-inferior efficacy was inadequate, derived from a post-hoc sub-group analysis;
- The evidence to support non-inferior harms was weak and inconsistent with trends observed in trial adverse event (AE) data; and,
- The claim of non-inferiority of afatinib compared to erlotinib and gefitinib was largely irrelevant for the proposed use of afatinib following previous EGFR TKI use, as erlotinib and gefitinib were not the appropriate comparators for this indication.

The PBAC considered that the claim of non-inferiority for afatinib compared to erlotinib and gefitinib for the proposed listing could not be justified using the evidence provided in this submission.

10. Economic Analysis

The submission undertook a cost-minimisation approach based on a non-inferiority claim for overall survival and for harm. The submission did not identify additional costs or cost offsets associated with the treatment of patients with afatinib compared to erlotinib and gefitinib.

The PBAC considered this economic approach was not supported due to the weakness of the clinical claim. For the treatment of patients who had had previous EGFR TKI therapy, the use of a cost-minimisation approach was inappropriate, as the drugs being used as comparators were not listed for use in the proposed indication.

11. Estimated PBS Usage and Financial Implications

A market share approach was used, in which afatinib substitutes for current and projected erlotinib and gefitinib scripts. The estimated total net cost to the PBS was less than $10 million for afatinib over the first 5 years

12. Recommendation and Reasons

The PBAC rejected the submission on the basis that the requested afatinib listing is outside its proposed TGA indication and that the evidence provided in the submission did not support the proposed afatinib listing in the submission.

The PBAC has advised in previous assessments of gefitinib (November 2012 PBAC meeting) that TKIs for NSCLC should be listed without specifying line of therapy.

Outcome

Rejected

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.