Public Summary Document

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

1. Purpose of Application

The submission requested PBS listing of afatinib as first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients with epidermal growth factor receptor (EGFR) gene mutation(s).

2. Background

Afatinib had not previously been considered by the PBAC. The PBAC considered that afatinib, a tyrosine kinase inhibitor like gefitinib or erlotinib, is codependent on EGFR mutation testing and so the PBAC found that the previous advice from Medical Services Advisory Committee (MSAC) in relation to EGFR mutation testing in the context of gefitinib and erlotinib was relevant. A corresponding minor submission to extend the current Medicare Benefits Schedule (MBS) listing of EGFR gene mutation testing to include afatinib was lodged for MSAC consideration.

The PBAC noted that submissions for two other EGFR TKIs, gefitinib and erlotinib, were also on its July 2013 meeting agenda for essentially the same restriction and so considered the three medicines in relation to each other.

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 November 2013 for 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

Authority required

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 (NSCLC) in patients with evidence of activating mutation(s) of the EGFR gene in tumour material, and WHO/ECOG performance status 0 to 2, who do not have progressive disease.

The PBAC mostly supported the requested listing in advising that a restriction for afatinib 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, i.e. L858R at exon 21 and exon 19 deletions, noting that MSAC had advised against this, as did the October 2012 EGFR/TKI stakeholder meeting 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 PBAC 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.

5. Clinical Place for the Proposed Therapy

The submission proposed afatinib monotherapy to replace the current most commonly used platinum-based doublet chemotherapy regimens as first-line treatment of non-squamous or NOS locally advanced (stage IIIB) or metastatic (stage IV) NSCLC in patients with evidence of activating mutation(s) of the EGFR gene.

6. Comparator

The comparator used in the economic model in the submission was no EGFR gene mutation testing and treatment with platinum-based doublet chemotherapy in patients with locally advanced or metastatic disease. Cisplatin/pemetrexed was used as the comparator in the key randomised trial (LUX Lung 3), but cisplatin/gemcitabine was used as an indirect comparator in the economic model. Indirect comparisons with gefitinib and erlotinib were also presented in the submission. A direct comparison with cisplatin/gemcitabine (LUX Lung 6) was provided in the Pre-Sub-Committee Response.

The PBAC accepted the comparators in the submission

7. Clinical Trials

AFATINIB VS PLATINUM-BASED DOUBLET CHEMOTHERAPY

The submission conducted an indirect comparison comparing afatinib with cisplatin + gemcitabine using a common reference of cisplatin + pemetrexed in two randomised open-label controlled trials:

- LUX Lung 3 which compared afatinib with cisplatin + pemetrexed, and
- Scagliotti et al (2008) which compared cisplatin + gemcitabine with cisplatin + pemetrexed. Inclusion criteria for this study did not require patients to have an EGFR mutation.

The Pre-Sub-Committee Response (PSCR) also presented an abstract of a direct comparison between afatinib and cisplatin+gemcitabine (LUX Lung 6).

AFATINIB VS EGFR TKIS (ERLOTINIB OR GEFITINIB)

The treatment effect of afatinib relative to either gefitinib or erlotinib was based on a multiple stepped indirect comparison. The treatment effect of afatinib relative to cisplatin/gemcitabine (derived from the indirect comparison of LUX Lung 3 vs Scagliotti et al) is compared to:

1) the pooled relative treatment effect of gefitinib vs platinum-based doublet chemotherapy (from four gefitinib trials with uncertain exchangeability: IPASS, Maemondo et al (2010), First-SIGNAL and Mitsudomi et al (2010)), and
2) the pooled relative treatment effect of erlotinib vs platinum-based doublet chemotherapy (from two erlotinib trials with uncertain exchangeability: EURTAC and OPTIMAL).

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
LUX Lung 3		
Yang JC-H et al	LUX Lung 3: A randomised, open-label phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harbouring EGFR-activating mutations.	ASCO Annual Meeting 2012; Abstract LBA7500.
Yang JC-H et al	Activity of afatinib in uncommon epidermal growth factor receptor (EGFR) mutations in LUX Lung 3, a Phase III trial of afatinib or cisplatin/pemetrexed in EGFR M+ lung cancer.	Annals of Oncology 2012; 23(Suppl. 9) ix410 Abstract 1252P.
Sequist LV	LUX Lung 3 Symptom control and health related quality of life results from a randomised phase III study in first-line patients with advanced NSCLC harbouring EGFR mutations.	Annals of Oncology 2012; 23(Suppl. 9) ix402 Abstract 1229PD.
Scagliotti et al		

Scagliotti GV et al	Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.	Journal of Clinical Oncology 2008; 26:3543-3551.
Scagliotti GV et al	Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaive patients with advanced non-small cell lung cancer: A risk-benefit analysis of a large phase III study.	European Journal of Cancer 2009; 45:2298-2303.
Syrigos KN et al	Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer.	Annals of Oncology 2010; 21:556-561.

For details of publications from IPASS and First-SIGNAL studies, refer to the gefitinib November 2012 Public Summary Document (PSD). For details of publications from EURTAC and OPTIMAL studies, refer to the erlotinib July 2012 PSD.

During the PSCR Boehringer Ingelheim provided supportive data from the LUX Lung 6 [Wu L-Y et al J. Clin. Oncol. 2013, 31(Suppl.) ASCO Meeting Abstract 8016]

8. Results of Trials

Overall survival (OS) - compared to platinum-based chemotherapy

The PBAC noted that updated overall survival data from a January 2013 cut-off (an additional 11 months of follow-up) of the LUX Lung 3 trial and an abstract of the recently completed LUX Lung 6 trial were provided in the Pre-Sub-Committee Response. The OS data from the LUX Lung 3 trial was not mature.

The PBAC noted that the median OS of afatinib arm was 28.06 months compared to 28.16 months of the chemotherapy arm in intent to treat (ITT) population (HR=0.907; 95% CI: 0.660, 1.246) in the updated LUX Lung 3 trial. The PBAC also noted the hazard ratio for OS (43% maturity) for afatinib chemotherapy (cispaltin/gemcitabine) in the recently completed LUX Lung 6 trial (HR=0.95)

Progression free survival (PFS) - compared to platinum-based chemotherapy

There was a statistically significant difference in progression free survival (PFS), determined by both central blinded (independent) assessment and non-blinded investigator assessment,

that favoured afatinib over cisplatin/gemcitabine for the ITT population and for the common mutations subgroup.

The afatinib point estimate of PFS risk reduction was greater:

- when estimated by investigator versus independent review in the common mutations subgroup (63% vs 58%) and the ITT population (56% vs 48%); and
- for the common mutations subgroup versus the ITT population when determined by investigators (63% vs 56%) and independent reviewers (58% vs 48%).

Independent review (Blinded assessment of PFS):

- ITT analysis: median PFS favoured afatinib over cisplatin/pemetrexed treatment (increment of 5.4 months) and the difference was statistically significant;
- Common vs "other" EGFR mutations subgroup: median PFS favoured afatinib over cisplatin/pemetrexed treatment and the difference was statistically significant. For this pre-specified subgroup of "other" EGFR mutations, the median PFS was substantially shorter in the afatinib arm compared with the chemotherapy arm (2.76 months vs 9.92 months; HR=1.892; 95% CI: 0.836, 4.279; p=0.1198).

Investigator review (Non blinded assessment of PFS):

- ITT analysis: there was a statistically significant difference in the median PFS favouring treatment with afatinib compared with cisplatin/pemetrexed treatment (HR=0.488; 95% CI: 0.367, 0.649; p<0.0001); and
- Common mutations subgroup: there was a statistically significant difference in the median PFS favouring treatment with afatinib compared with cisplatin/pemetrexed treatment (12.68 months vs 6.28 months; HR=0.412; 95% CI: 0.307, 0.552; p<0.0001). No analyses are provided for the "other" EGFR mutations subgroup.

The PBAC noted that the PSCR presented some results from the recently completed LUX Lung 6 trial, which also supported a statistically significant difference in the median PFS favouring treatment with afatinib compared with cisplatin/gemcitabine treatment.

<u>Progression free survival (PFS) - compared to other TKIs</u>

The PBAC noted that there were no head-to-head trials of afatinib versus other TKIs. The indirect comparisons resulted in 95% confidence intervals that did not exclude inferiority, were wide and were difficult to interpret. While noting the limitations of a multi-step indirect comparison, some of the indirect comparisons favoured erlotinib over afatinib. No non-inferiority margin(s) or minimal clinically important difference(s) (MCID) were proposed to support a claim of non-inferiority of afatinib compared to other TKIs.

The results for the summary of the indirect treatment comparison afatinib versus gefitinib for the outcome of PFS (rounded to two decimal places) are shown in the following table:

	Afatinib vs standard doublet chemotherapy HR (95%CI)	**Gefitinib versus standard doublet chemotherapy**		
		Doublet chem N	**Gefitinib N**	**Gefitinib vs doublet chem HR (95%CI)**
Afatinib versus standard doublet chemotherapy (cisplatin/gemcitabine) by ITT or subgroup categories defined in LUX Lung 3				
Independent review				
ITT	**0.52, (0.37, 0.72)**			
Common mutations	**0.42, (0.30, 0.60)**			
Investigator review				
ITT	**0.44, (0.32, 0.60)**			
Common mutations	**0.37, (0.27, 0.51)**			
Gefitinib versus standard doublet chemotherapy				
Mok 2009 IPASS		129	132	**0.48, (0.36, 0.64)**
Maemondo 2010		114	114	**0.30, (0.22, 0.41)**
Mitsudomi 2010		86	86	**0.49, (0.34, 0.71)**
Han 2012		16	26	0.54, (0.27, 1.1)
Meta-analysis gefitinib trials				
Fixed effects		345	358	**0.42, (0.35, 0.50)**
Random effects		345	358	**0.42, (0.32, 0.56)**
Indirect comparison afatinib versus gefitinib, HR (95%CI)				
Independent review				
ITT-Fixed effects	1.24, (0.85, 1.80)			
ITT-Random effects	1.24, (0.80, 1.91)			
Common mutations (fixed effects)	1.01, (0.69, 1.48)			
Common mutations (random effects)	1.01, (0.65, 1.57)			
Investigator review				
ITT-Fixed effects	1.04, (0.73, 1.50)			
ITT-Random effects	1.04, (0.69, 1.59)			
Common mutations (fixed effects)	0.88, (0.61, 1.27)			
Common mutations (random effects)	0.88, (0.58, 1.35)			

Chem=Chemotherapy; Cis/gem=Cisplatin/gemcitabine; **Figures in bold indicate significant results.**

The results for the summary of the indirect treatment comparison afatinib versus erlotinib for the outcome of PFS (rounded to two decimal places) are shown in the following table:

	Afatinib vs standard doublet chemotherapy HR (95%CI)	**Erlotinib versus standard doublet chemotherapy**		
		Doublet chem N	**Erlotinib N**	**Erlotinib vs doublet chem HR (95%CI)**
Afatinib versus standard doublet chemotherapy (cisplatin/gemcitabine) by ITT or subgroup categories defined in LUX Lung 3				
Independent review				
ITT	**0.52, (0.37, 0.72)**			
Common mutations	**0.42, (0.30, 0.60)**			
Investigator review				
ITT	**0.44, (0.32, 0.60)**			
Common mutations	**0.37, (0.27, 0.51)**			
Erlotinib versus standard doublet chemotherapy				
Rosell 2012 EURTAC		87	86	**0.37, (0.25, 0.54)**
Zhou 2011 OPTIMAL		72	82	**0.16, (0.10, 0.26)**
Meta-analysis erlotinib trials				
Fixed effects		159	168	**0.27, (0.20, 0.36)**
Random effects		159	168	**0.25, (0.11, 0.56)**
Indirect comparison afatinib versus erlotinib, HR (95% CI) (EURTAC only for erlotinib)				
Independent review				

ITT	1.40 (0.84, 2.33)
Common mutations	1.15 (0.69, 1.92
Investigator review	
ITT	1.19 (0.72, 1.95)
Common mutations	1.00 (0.61, 1.66)
Indirect comparison afatinib versus erlotinib, HR (95% CI) (Pooled across EURTAC and OPTIMAL for erlotinib), HR (95%CI)	
Independent review	
ITT-Fixed	**1.92 (1.23, 2.99)**
ITT-Random	2.07 (0.86, 5.00)
Common mutations-Fixed	1.57 (1.00, 2.46)
Common mutations-Random	1.70 (0.70, 4.10)
Investigator review	
ITT-Fixed	**1.63 (1.06, 2.50)**
ITT-Random	1.76 (0.73, 4.20)
Common mutations-Fixed	1.37 (0.89, 2.12)
Common mutations-Random	1.48 (0.62, 3.56)

. **Figures in bold indicate significant results.**

The PBAC considered that for afatinib, as seen with the other TKIs (erlotinib and gefitinib), there is no evidence of a survival benefit in the treatment of NSCLC compared to platinum-based chemotherapy. The PBAC accepted that there was a statistically significant benefit for afatinib monotherapy over platinum-based chemotherapy in terms of an additional median progression-free survival of approximately 6.4 months (LUX Lung 3 common mutation population) or 5.4 months (LUX Lung 6 ITT population) compared to platinum chemotherapy.

The PBAC considered that it is difficult to conclude whether afatinib is non-inferior in terms of effectiveness compared to gefitinib or erlotinib 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 afatinib, erlotinib and gefitinib 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 afatinib 40 mg daily, erlotinib 150 mg daily and gefitinib 250 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.

With regard to comparative harms, the PBAC noted that there were no direct comparative data and that no formal indirect comparisons were presented by the submission to assess the comparative safety of afatinib relative to either cisplatin/gemcitabine or gefitinib or erlotinib.

The PBAC noted that there were relatively high rates of adverse events (AEs) associated with afatinib relative to doublet platinum chemotherapy, including more Grade 3 or higher AEs, in the LUX Lung 3 trial. There was a higher proportion of dose reductions during treatment with afatinib compared to treatment with either gefitinib or erlotinib, although there were limitations for those indirect comparisons.

The PBAC agreed that the TKIs have slightly different toxicity profiles (e.g. 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

For the comparator of platinum based doublet chemotherapy, the submission claimed that afatinib is superior and presented a cost-effectiveness analysis.

The PBAC noted that the comparator (cisplatin/pemetrexed) for afatinib in LUX Lung 3 may be a more effective chemotherapy doublet compared to other platinum-based chemotherapy (i.e. carboplatin/paclitaxel or cisplatin/gemcitabine). 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 agreed that the data did suggest a statistically significant PFS benefit in favour of afatinib over chemotherapy. However, the PBAC also considered that:

- The benefit of afatinib was due only to a prolongation of progression free survival which is associated with some improvement in quality of life; there was no observed benefit in overall survival. The results from the LUX Lung 3 trial, in which the cross-over of patients following progression could be considered a comparison of access to afatinib first-line vs access to an EGFR TKI second-line for EGFR M+ patients, did not indicate any gain in OS (OS data remain immature); and
- Many serious adverse events including grade 3 or higher appeared more often in the afatinib arm compared to the cisplatin/pemetrexed arm.

For the comparators of gefitinib or erlotinib, the submission claimed that afatinib is non-inferior and presented a cost-minimisation analysis for this comparison.

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

10. Economic Analysis

The submission presented a modelled economic evaluation (cost-utility analysis in terms of incremental cost per QALY gained) based on the superiority claim over platinum based doublet chemotherapy. That is, that EGFR testing and first-line access to afatinib for mutation positive patients is superior to the current situation where neither EGFR testing nor afatinib are available at diagnosis. The submission presented an ICER in the range of $45,000 – $75,000/QALY based on the observed and extrapolated PFS and OS of afatinib in LUX Lung 3, compared to cisplatin/gemcitabine based on an indirect comparison using Scagliotti et al. Outcomes were extrapolated from data at maximum follow-up of 22 months observed in LUX Lung 3, with a 5 year time horizon applied in the model. Utility weights measured from LUX Lung 3 and LUCEOR 2 (which investigated health-related quality of life in advanced NSCLC patients) trials were applied, along with utility decrements from studies

conducted in patients receiving second or third-line therapy (LUX Lung 1 and Tabberer et al).

The superiority claim was based on an indirect comparison of trials. The PBAC noted that the following translation issues were not properly addressed and could have affected the economic analysis:

- the frequency of EGFR mutations in Australian non-squamous or NOS NSCLC patients
- the proportion of NSCLC patients diagnosed at Stage IIIb/IV disease, and time to disease progression
- the treatment effect of TKIs in EGFR M+ Asian versus Caucasian patients
- the inclusion of maintenance therapy in the comparator arm
- the number of cycles of comparator treatment
- the extrapolation of trial PFS and OS data beyond the trial period
- the fit and extrapolation of PFS and OS data for the indirect comparator
- the selection of utility weights
- the relationship between PFS and OS
- the selection of treatment options following first-line therapy failure
- the estimation of costs and outcomes associated with treatment following first-line failure.

The PBAC noted that the submission did not consider the prognostic impact of EGFR mutation status and the economic model assumes 100% specificity and sensitivity. The PBAC also noted that the submission did not explore the quantitative impact of false positives and false negatives in the economic evaluation. It also did not explore any variation in the base case prevalence of 15% for tested patients being EGFR positive.

For patients with non-squamous or NOS NSCLC, the modelled evaluation compared:

- the proposed management (intervention) of EGFR testing to guide first-line therapy appropriately with either afatinib (EGFR M+) or platinum-based chemotherapy (EGFR M-), versus;
- the current management (comparator) of platinum-based chemotherapy in the first-line setting without EGFR testing.

The submission presented two base case analyses: one that assumed and one that did not assume maintenance therapy in the comparator arm. The submission argued that the maintenance therapy scenario was “more reflective of current clinical practice in Australia”. The maintenance scenario included costs, but not benefits, associated with pemetrexed therapy. The PBAC recalled that it had previously rejected this approach in the consideration of erlotinib for first-line treatment of NSCLC (PBAC Erlotinib Public Summary Document (PSD), July 2012).

Three health states were considered for Stage IIIb/IV NSCLC patients entering the model; progression-free, progressive disease and death. The PFS and OS data from the afatinib arm of the LUX Lung 3 trial (which compared afatinib to cisplatin + pemetrexed) were extrapolated to 10 years from a maximum duration of 22 months’ follow-up data using a Weibull distribution. A 5 year time horizon was used in the base case.

The progression free survival (PFS) and overall survival (OS) data for the comparator arm (cisplatin + gemcitabine) were mathematically derived based on the afatinib PFS and OS data using the hazard ratio for the indirect comparison calculated in Section B.6 in the submission.

The PFS data informed the proportion of patients in the progression-free health state, with that in the death state informed by the OS data; the progressive disease state was informed by the difference in OS and PFS. The OS data from LUX Lung 3 was considered immature at the time of the interim analysis.

The base case analysis used PFS by investigator review, rather than by independent review. The investigator measures were prone to observer bias.

All patients entered the economic model in the progression-free state:

- In the proposed management (intervention) arm of the economic model, all patients were tested for EGFR mutation status on diagnosis, and upon presentation of Stage IIIb/IV disease, EGFR M+ patients were treated with afatinib until disease progression, and patients who were EGFR M-/unknown received five cycles of cisplatin + gemcitabine. A one-off incremental cost was added for the cost of the EGFR test, re-biopsy and adverse events related to re-biopsy;
- In the current management (comparator) arm of the economic model, upon presentation of Stage IIIb/IV disease, all patients were treated with five cycles of cisplatin + gemcitabine. No EGFR testing was assumed in the first-line setting. The use (and costs) of the comparator arm were overestimated, as four cycles of platinum doublet chemotherapy are recommended in Australian current practice.

The PBAC noted a large utility decrement from progression free to progression in the model. Such a large decrement from progression-free to progressive disease was not supported by the LUX Lung 3 EQ-5D utility data, which were provided in an attachment to the Pre Sub – Committee Response (table from the CSR where the decrement was very little in both treatment arms during the 39 weeks of treatment. The PBAC noted that the generated QALYs were not supported by clinical data and that, of the range of potential utilities associated with the health states of the model identified by the submission, only those that favour afatinib were used. In particular, the size of the utility decrement, which was not supported by the LUX Lung 3 utility data, was the main driver of the cost-effectiveness in this submission.

The PBAC noted that the treatment sequences used in the economic model included second-line erlotinib use in EGFR wild type patients. The PBAC noted that this second-line use may not be reasonable and considered that it was inconsistent with the consensus view of the October EGFR/TKI stakeholder meeting.

The model assumed that all patients who progressed would receive a second-line treatment. As highlighted by ESC, the PBAC noted that in a sample of Medicare Australia data, only 45% of patients who were currently receiving first-line treatment would go on to receive second-line therapy (PBAC Gefitinib PSD, November 2012).

The PBAC noted that incremental cost/extra QALY gained and the incremental cost/extra LY gained of the stepped economic evaluation, for the base case without pemetrexed maintenance were $45,000 - $75,000 and $105,000 - $200,000 respectively. The PBAC also

noted that, for the submission's preferred base case with pemetrexed maintenance, the results were dominant.

The incremental benefits of EGFR testing for access to afatinib were all achieved in the small proportion of modelled patients who test EGFR M+ (16%) and therefore the absolute benefit in these patients was substantially greater (approximately 6x) than the apparent incremental benefit observed across the whole modelled population.

The incremental benefits were likely to be overestimated due to the use of PFS measured by investigator review, rather than independent review, and the choice of utility in the progression-free health state. Overall, the ICER without pemetrexed maintenance was likely to be underestimated for these reasons.

However, the PBAC also accepted the reality that listing afatinib 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 PBAC noted that ±25% of the mean value was used as upper and lower limits in most sensitivity analyses presented in the submission. The PBAC considered that this was not appropriate as it narrowed the variation of the ICER. The 95% CI was used during the evaluation to revise the sensitivity analysis.

11. Estimated PBS Usage and Financial Implications

The PBAC considered the submission's estimate of likely patient number to be an underestimate. The submission estimated a net cost per year to the PBS 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.

The PBAC accepted the Drug Utilisation Sub-Committee (DUSC) advice in relation to afatinib with regard to the likely number of EGFR mutation positive patients over the first five years of listing. The PBAC also accepted the DUSC advice that the net cost to the Government is highly sensitive to the duration of therapy noting that the cost for afatinib could rise from $30 million - $60 million to $60 million - $100 million if the duration of therapy is increased from 12 months to 24 months.

The PBAC noted that the sponsor proposed a confidential risk share arrangement.

12. Recommendation and Reasons

The PBAC advised that a restriction for afatinib 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 accepted that the comparator for afatinib 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 afatinib 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 afatinib 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 suggests 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 (i.e. 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 afatinib, 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 + gemcitabine chemotherapy without first-line EGFR testing.

The modelled cost-utility analysis of afatinib 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 in the range of $45,000 - $75,000/QALY (excluding maintenance treatment with pemetrexed before disease progression). The PBAC recalled that in July 2012, in the context of considering a similar submission for erlotinib, it had expressed concerns 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 afatinib 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 PBAC noted that a significant limitation of the afatinib model is its failure to account for false positive EGFR test results, or for any variation in the base case prevalence of 15% for tested patients being EGFR mutation positive. The PBAC noted that both would increase the ICER, but also considered that while this would better estimate the ICER for the entire NSCLC population which is tested, it would underestimate the per patient clinical benefit to the EGFR mutation positive cohort which is treated.

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

- the generated QALYs were not supported by clinical data
- the assumption that all patients receiving first-line chemotherapy who progress will receive a second-line treatment was inconsistent with Medicare data, which suggests that only 45% of patients will go on to receive subsequent treatment
- of the range of potential utilities associated with the health states of the model identified by the submission, only those that favour afatinib were used
- the utility decrement between stable and progressive disease was not supported by the LUX Lung 3 utility data
- the assumption that EGFR mutation negative patients in the comparator arm will receive erlotinib in second line may not be reasonable.

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

The PBAC noted that the applicant had requested flat pricing. The PBAC considered that a more appropriate basis for pricing would be a reduced price for a reduced strength. The PBAC considered that a lower price would be more appropriate for consideration.

The PBAC noted discrepancies in the estimated utilisation patterns and net cost to the PBS across the three submissions and agreed with the reasons for these differences as outlined in the DUSC advice. The PBAC agreed with the advice received during the evaluation that the number of patients with NSCLC who test positive for an EGFR mutation 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 afatinib 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 noted and welcomed the input received from health care professionals via the Consumer Comments facility on the PBS website. Most notably, comments cited improvement in less hospital visits for I.V chemotherapy, less toxicity and superior control of symptoms as benefits associated with treatment with afatinib.

The PBAC deferred the submission in order to ascertain whether the applicant is prepared to offer a reduced price and if so, to consider the implications of this reduced price for revising the cost-effectiveness of listing afatinib as indicated by the PBAC.

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. The PBAC also deferred the submission in order to await the advice of the TGA Delegate on the application to register afatinib.

The PBAC considered that a major re-submission would be required if the applicant wished to seek a higher effective 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.

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

Recommended Listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
AFATINIB DIMALEATE				
Tablet 20 mg	28	3	Giotrif®	Boehringer Ingelheim Pty Limited
Tablet 30 mg	28	3		
Tablet 40 mg	28	3		
Tablet 50 mg	28	3		

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 been treated with any EGFR tyrosine kinase inhibitor (TKI), **OR** The patient must have developed intolerance to another TKI of a severity necessitating permanent treatment withdrawal; **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
AFATINIB DIMALEATE			
Tablet 20 mg	28	3	Giotrif® Boehringer Ingelheim Pty Limited
Tablet 30 mg	28	3	
Tablet 40 mg	28	3	
Tablet 50 mg	28	3	

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 afatinib.
Clinical criteria:	The patient must not have progressive disease.

Outcome:
Defer

Subsequent to the meeting, the sponsor offered to reduce its price, as had been requested by the PBAC, for the 40mg strength of afatinib under the proposed restriction to patients with NSCLC who are EGFR mutation positive. The prices of the other strengths were calculated according to standard Pharmaceutical Benefits Pricing Authority methodology. The PBAC

considered that the sponsor's offer was in line with that already accepted at its out of session recommendation for erlotinib.

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.

The PBAC considered that, at the reduced price, afatinib could be considered to be cost-effective in comparison with platinum-based doublet chemotherapy, based on afatinib'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 afatinib over chemotherapy in patients with NSCLC who are EGFR mutation positive.

The PBAC therefore recommended, out of session, the PBS listing of afatinib on a cost minimisation basis with erlotinib. The equi-effective doses were afatinib 40mg to erlotinib 150mg, based on the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration

The PBAC recommended afatinib 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. Afatinib is to cease on disease progression. The PBAC recommended that the PBS restriction exclude the possibility of sequential use of other TKIs following failure of afatinib.

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. Additionally the risk-share arrangement should facilitate additional research into the diagnosis and treatment of patients with EGFR mutations.. The data from the research should be placed into the public domain for use by researchers, government and industry alike.

<u>Advice to the Minister under Subsection 101(3BA)</u>
In accordance with subsection 101(3BA) of the National Health Act 1953 ('the Act'), the PBAC advised that it is of the opinion that, on the basis of the material available to its July 2013 meeting, afatinib should be treated as interchangeable on an individual patient basis with erlotinib and gefitinib. In forming this view the PBAC considered the current indication common to all three drugs (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).

Outcome:
Recommend

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

Boehringer Ingelheim continues to work with the PBAC to ensure the PBS listing of afatinib for patients with NSCLC.