PUBLIC SUMMARY DOCUMENT
Product: Gefitinib, tablet, 250 mg, Iressa®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought a first-line listing for gefitinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (Stage IIb/IV NSCLC) who have an activating mutation in the epidermal growth factor receptor gene (EGFR M+).

2. Background

Gefitinib is currently PBS listed for the treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with a WHO performance status of 2 or less, where disease progression has occurred following treatment with at least one chemotherapy agent and there is evidence that the patient has an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material.

Gefitinib was recommended for listing at the July 2004 meeting of the PBAC on the basis of acceptable cost-effectiveness compared with docetaxel and best supportive care for patients with an activating mutation of the EGFR gene. Listing was effective from 1 December 2004.

At the March 2008 meeting, the PBAC considered a sponsor request to amend the PBS restriction by removal of the requirement for the activating EGFR mutation and alignment with the TGA indication at that time, which specified two patient subgroups eligible for gefitinib: those who have never smoked and those taking gefitinib who have demonstrated some benefit. The PBAC considered that inadequate evidence was provided to allow an assessment to be made on the cost-effectiveness of gefitinib in the population that would be covered under the requested listing and that more detailed information from a recent clinical trial was required. PBAC therefore recommended no changes be made to the PBS listing for gefitinib pending a further submission from the sponsor.

At its November 2009 meeting, the PBAC recommended an amendment to the current PBS restriction by removing the requirement that analysis of the DNA sequence of the EGFR gene must be used to detect a mutation in the EGFR gene. The PBAC noted that the analysis by DNA sequencing methodology was not MBS reimbursed and it was therefore considered reasonable to use other methodologies to detect the specific activating mutations in the EGFR gene.

3. Registration Status

Gefitinib has been TGA registered since 28 April 2003. The TGA registration for gefitinib was revised on 12 July 2010. It is currently indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer (NSCLC), whose tumours express activating mutations of the EGFR tyrosine kinase.

4. Listing Requested and PBAC's View

Authority Required

Initial PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with an activating mutation of the EGFR gene.

The authority application can be made over the telephone if a pathology report shows the presence of activating mutation(s) of the EGFR gene from an Approved Pathology Authority. A copy of this report and the gefitinib (Iressa) PBS Authority application for use in the treatment of NSCLC form must be sent to: Medicare Australia Reply Paid 9826 GPO Box 9826 Hobart TASMANIA.

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

NOTE:
No applications for increased maximum quantities and/or repeats will be authorised.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The submission proposed that gefitinib is an alternative to chemotherapy in the treatment of patients with EGFR mutation positive non-small cell lung cancer.

6. Comparator

The comparator proposed by the submission was platinum based chemotherapy. The submission stated that the combination of carboplatin and gemcitabine was the most commonly used regimen in Australia, but other platinum-based doublet chemotherapy regimens were also used. The pivotal trial evidence (IPASS) compared gefitinib with carboplatin and paclitaxel.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The key evidence presented in the submission was one of multiple pre-planned exploratory sub-group analyses (of EGFR mutation positive (M+) patients) of the Iressa Pan Asia Study (IPASS) randomised controlled trial, where gefitinib was compared to carboplatin plus paclitaxel, as first-line treatments, in patients with locally advanced or metastatic NSCLC, with adenocarcinoma (including bronchoalveolar carcinoma).

Three supportive first-line randomised trials (NEJ002, Study 0054 and WJTOG 3405) were also presented in the submission although the trial results were not yet fully available. NEJ002, Study 0054 and Study WJTOG 3405 respectively compared gefitinib to carboplatin plus paclitaxel, cisplatin plus gemcitabine or cisplatin plus docetaxel. The NEJ002 study was only conducted in EGFR M+ patients, while an exploratory sub-group analysis of EGFR M+ patients was conducted in Study 0054 to provide support for the requested restriction. Study WJTOG 3405 was conducted in EGFR M+ patients, with inclusion criteria specific for Exon 19 deletion and Exon 21 L858R activating mutations. All studies presented in the submission were conducted in Asian populations. The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Key direct randomised trial		
Iressa Pan Asia		

Study (IPASS) Mok TS, et al.	Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma.	N Engl J Med 2009; 361(10): 947-57
Supplementary randomised trials		
North East Japan 002 Study (NEJ002) Kobayashi K, et al	First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (PTS) with EGFR mutations: A phase III study (002) by North East Japan Gefitinib Study Group	J Clin Oncol 2009 24[15s]
Inoue A, et al	A randomized phase III study comparing gefitinib with carboplatin (CBCDA) plus paclitaxel (TXL) for the first-line treatment of non-small cell lung cancer (NSCLC) with sensitive EGFR mutations: NEJ002 study	Abstract available at www.ecco-org.eu/Conferences-and-Events/ECCO-15-ESMO-34/page.aspx/216 (accessed 4 January 2011)
Study 0054 (Korean) Lee JS, et al	A Randomized Phase III Study of Gefitinib (IRESSA) versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung.	J Thor Oncol 2009 4[9], Supp 1.
WJTPG3405 Mitsudomi T, et al	Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.	Lancet Oncology 2010; 11(2): 121-8
Tsurutani J, et al	A phase III, first-line trial of gefitinib versus cisplatin plus docetaxel for patients with advanced or recurrent non-small cell lung cancer (NSCLC) harbouring activating mutation of the epidermal growth factor receptor (EGFR) gene.	Abstract available at www.ecco-org.eu/Conferences-and-Events/ECCO-15-ESMO-34/page.aspx/216 (accessed 4 January 2011)

8. Results of Trials

The primary outcome of IPASS was progression-free survival in the overall population. The outcome of interest in the submission was the pre-specified exploratory analysis of progression-free survival (PFS) in the EGFR M+ subgroup of patients. The key results are summarised in the following table.

Results of progression-free survival (in months) across the direct randomised trials (Hazard ratios rounded to two decimal places)

Trial ID	Gefitinib Median (95% CI) months	Carboplatin + paclitaxel Median (95% CI) months	Absolute difference (months)	Hazard ratio (between treatment comparison) (95% CI)
IPASS				
ITT (all patients randomised)	N = 609 5.7	N = 608 5.8	-0.1	0.74* §§ (0.65, 0.85)
EGFR M+ subgroup	**N = 132 9.5 (8.0, 11.2)**	**N = 129 6.3 (5.6, 7.0)**	**3.2**	**0.48* (0.36, 0.64)**
EGFR M- subgroup	N = 91 1.5 (NR)	N = 85 5.8 (NR)	-4.3	2.85* (2.05, 3.96)
NEJ002 (all EGFR M+)				
Per protocol population	**N = 114 10.8 (NR)**	**N = 110 5.4 (NR)**	**5.4**	**0.30** (0.22, 0.41)**
Study 0054				
	Gefitinib	**Cisplatin + gemcitabine**		
EGFR M+ subgroup	**N = 26 8.4 (NR)**	**N = 16 6.7 (NR)**	**1.7**	**0.61^ (0.31, 1.22)**
EGFR M- subgroup	N = 27 2.1 (NR)	N = 27 6.4 (NR)	-4.3	1.52^^ (0.88, 2.62)
WJTOG 3405 (all EGFR M+)				
	Gefitinib	**Cisplatin + docetaxel**		
Per protocol population	**N = 86 9.2 (8.00, 13.90)**	**N = 86 6.3 (5.80, 7.80)**	**2.9**	**0.49* (0.34, 0.71)**

Bolded: EGFR M+ population.

* p<0.0001; ** p<0.001; ^ p = 0.084; ^^ p = 0.071.

§§ The HR was not constant over time, with the probability of being progression free in favour of carboplatin / paclitaxel doublet chemotherapy in the first 6 months, and in favour of gefitinib in the following 16 months. In such a case, the use of HR is not valid. This was not the case for EGFR M+ mutation status.

CI = Confidence interval; NR = Not reported; ITT = Intention to treat; PP = per protocol; HR = hazard ratio.

The PBAC noted that an examination of the IPASS PFS data from EGFR M+ and EGFR M- patients in the chemotherapy arm (there are limited data to fully assess comparability of the EGFR groups) did not indicate there was a prognostic effect, independent of treatment effect, associated with EGFR mutational status (although it is documented in the literature that some EGFR mutation types are independent prognostic factors). The results for median PFS in the carboplatin plus paclitaxel arm for EGFR M+ patients and EGFR M- patients were similar (6.3 months and 5.8 months respectively). For the doublet chemotherapy treatment arms, there was a higher proportion of EGFR M- patients 1) with a WHO performance status of 2 or were in bed greater than or equal to 50% of the time (11% vs 5%), 2) who were ex-smokers (9% vs 5%) and 3) who had metastatic disease (84% vs 78%) compared to EGFR M+ patients. These were important prognostic factors for survival in NSCLC. However, tumour burden and histology did not appear to differ substantially between EGFR M+ and

EGFR M- patients in the treatment arms. The extent of any confounding on the relative PFS estimates observed in the EGFR subsets allocated to chemotherapy, remained uncertain from the available data.

Overall survival (OS) data were also reported in the submission, although premature. From the updated OS data provided in the Pre-Sub-Committee response, the possibility of an independent prognostic effect of EGFR M+ unrelated to treatment could not be ruled out (although such an effect was not observed with the PFS data). It was possible that the observed differences in OS between the EGFR M+ and EGFR M- groups were the result of EGFR M- patients having fewer treatment options.

Gefitinib had a different toxicity profile to that of platinum-based chemotherapy; overall, serious adverse events appeared to be less common with gefitinib than with chemotherapy. Adverse effects reported to occur with greater frequency with gefitinib treatment included: eye disorders, hepatobiliary disorders, infections, injury/poisoning events, abnormal findings on laboratory investigations and renal/urinary disorders. An increased risk of interstitial lung disease associated with gefitinib which had been previously identified was also described.

For PBAC's view, see Recommendation and Reasons

9. Clinical Claim

The submission described gefitinib as superior in terms of comparative effectiveness and superior in terms of comparative safety over platinum-based chemotherapy in EGFR M+ patients. The superiority claim was based on PFS. The PBAC recalled that the claim of any overall survival advantage was not supported by the more mature data provided with the Pre-Sub-Committee response.

10. Economic Analysis

A modelled economic evaluation of advanced/metastatic NSCLC was presented.

Considering the updated data from IPASS showed no statistically significant improvement in overall survival for first-line gefitinib over first-line chemotherapy which allowed second-line gefitinib, the model's estimate of the incremental survival benefit (0.152 life-years gained) did not reflect the updated data from the most relevant available trial.

While the model appropriately incorporated costs and utility decrements for adverse events associated with first-line treatment, the submission neglected to include corresponding costs and utility decrements for adverse events associated with second-line treatment. These were likely to differ in the treatment arms, as patients receiving gefitinib first-line were assumed to receive chemotherapy after progression, while those initially receiving chemotherapy were assumed to subsequently receive gefitinib second-line. The Pre-Sub-Committee response reiterated that costs of adverse events and quality of life decrements were not able to be modeled in the second-line treatment position as there were no data available to inform the model. The response concluded that the use of gefitinib in the first-line treatment position was expected to be cost-effective as the use of gefitinib followed by chemotherapy was similar in treatment costs to chemotherapy followed by gefitinib. Patients have a small quality of life gain with the initial use of gefitinib compared to initial use of chemotherapy, though recent data indicate that there was no survival gain.

The incremental cost per extra quality adjusted life year (QALY) gained in the submission was in the range of $15,000 - $45,000. If 61% of patients received second-line therapy the incremental cost per extra QALY gained increased to be in the range of $75,000 – $105,000.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the submission to be less than $10 million per year in Year 5.

For PBAC's view, see Recommendation and Reasons

12. Recommendation and Reasons

The PBAC noted that the request for first-line listing would increase the number of eligible patients beyond the current listing. It agreed with the proposed use of gefitinib as being monotherapy, and that the main comparator would be a platinum-based doublet chemotherapy. Carboplatin and paclitaxel was accepted as a representative doublet, including for carboplatin and gemcitabine, the most widely used regimen in Australia.

The PBAC accepted that the most relevant direct randomised trial was IPASS. The results of three other relevant direct randomised trials (NEJ002, Study 0054 and WJTOG 3405) were not yet fully available but broadly support the IPASS results. The trial design allowed for switching such that patients randomised initially to chemotherapy could later commence gefitinib and patients randomised initially to gefitinib could later commence chemotherapy. The former arm represented current clinical practice because gefitinib was currently available second-line, and the latter arm represented clinical practice with first-line gefitinib as requested, so an ITT analysis including switching was a relevant comparison. In the trial, about 50% of patients received an alternative treatment (49% of patients randomised to gefitinib received subsequent carboplatin and paclitaxel treatment and 52% of patients randomised to carboplatin and paclitaxel received subsequent EGFR tyrosine kinase inhibitor treatment including gefitinib). This was similar to the submission's estimates that 30% of current second-line treatment was an EGFR tyrosine kinase inhibitor treatment and that 50% of patients would receive second-line treatment after first-line gefitinib.

One source of concern in applying the trial results to the Australian population was that, of 1217 randomised patients, only 437 (36%) provided tissue samples that were evaluable for mutation testing. Of the remaining 64%, 179 (15%) did not provide consent for biomarker analyses, 355 (29%) provided consent, but tissue samples were not obtained, and 246 (20%) provided samples that did not give an evaluable result. The proportion of Australian patients that would provide evaluable tissue samples was not known.

Another source of concern was that the primary evidentiary basis for the submission was one of multiple prespecified exploratory subgroup analyses, focussing on EGFR mutation positive (M+) patients of the IPASS trial. Further, in the subgroup of 437 patients with evaluable samples, 261 (60%) were M+, which is a much higher proportion than in unselected Australian non-small cell lung cancer (NSCLC) patients (9.5% estimated in the submission).

This concern was further complicated because IPASS (like the supportive trials) was enriched so that, compared with an unselected Australian population presenting with NSCLC, there were higher proportions of Asians (97.7% vs. 8% of Asian descent in Australia), females

(81% vs. 41%), never smokers (93.9% vs. 15% never smokers or passive smokers), younger (median age 57 years vs. 72 years) and non-squamous histology tumours (100% adenocarcinoma or bronchioalveolar vs. approximately 45% adenocarcinoma or unspecified). Although there was a higher proportion of EGFR activating mutations in this enriched population, the evidence available was not sufficient to determine whether these other patient characteristics may also independently modify the comparative treatment effect of first-line gefitinib beyond the modification attributed to the status of the EGFR mutation. In other words, there was little direct evidence for patients with EGFR activating mutations who were non-Asians, males, smokers, older and/or who had squamous or uncertain histology tumours.

In the subgroup of 437 IPASS patients providing evaluable EGFR mutation results, gefitinib statistically significantly extended progression-free survival (PFS) compared with carboplatin and paclitaxel in EGFR M+ patients (HR 0.48, 95% CI: 0.36, 0.64; median PFS 9.5 months compared with 6.3 months). By contrast, gefitinib statistically significantly reduced progression-free survival compared with carboplatin and paclitaxel in EGFR M- patients (HR 2.85, 95% CI: 2.05, 3.96; median PFS 1.5 months compared with 5.8 months). The PBAC accepted that these results supported the conclusion of first-line gefitinib treatment effect modification by EGFR mutation status for PFS.

In the subgroup of EGFR M+ patients, updated overall survival (OS) data (78% maturity) showed no difference between those initially randomised to gefitinib and those initially randomised to carboplatin and paclitaxel (HR 1.0, 95% CI: 0.76, 1.33; median OS 21.6 months compared with 21.9 months). As already noted, these ITT analyses were relevant to the requested listing and did not support the claim of an overall survival advantage for gefitinib generated by the submission's model (0.09 years for the deterministic model or 0.152 years for the probabilistic model). The PBAC therefore concluded that the submission's estimate of first-line gefitinib's overall effectiveness was an overestimate and its estimate of first-line gefitinib's cost-effectiveness was therefore also more favourable than was supported by the evidence provided.

In the absence of an improvement in overall survival with first-line gefitinib, the therapeutic advantages for first-line gefitinib related to quality of life improvements, due to difference in adverse event profiles, oral therapy rather than intravenous therapy and possibly due to prolonged progression free survival. The net impact of such quality of life improvements on improving quality-adjusted survival cannot be estimated from the model in isolation from the model's projected advantages in overall survival.

In relation to testing, the PBAC affirmed that the mutation testing in any PBS restriction should be limited to tumour material because this was supported by the trial evidence available, and should not be extended to possible alternative sample options such as sputum or pleural fluid. In addition, the PBAC advised that mutation testing should be restricted to detecting exon 19 deletions and exon 21 L858R point mutations because (a) these account for 247/261 (95%) of patients with the mutations detected and (b) some resistance mutations such as exon 20 T790M have already been documented.

Although the test used in determining EGFR mutation status was a commercially available dideoxy sequencing test, the PBAC advised that it would not be necessary to specify this particular test in any PBS or MBS restriction. Rather a minimal performance of eligible tests should be specified in terms of analytical validity, in order to minimise both false positives

and false negatives. The sensitivity and specificity of the EGFR tests affects the cost-effectiveness and these aspects are the subject of an ongoing assessment by the Medical Services Advisory Committee (MSAC).

An additional effect was that a lower prevalence of EGFR M+ made the cost-effectiveness less favourable by increasing the number of tests required to detect one patient who is EGFR M+ and so eligible for first-line gefitinib as requested. Although this latter effect of reduced prevalence was included in estimating the costs of testing the extent that prevalence was still overestimated influenced the extent to which submission's estimates still favoured first-line gefitinib.

A further concern in relation to testing was that, of 683 patients providing samples, 246 (36%) did not provide an evaluable result. This compared to estimates of approximately 5% in the Peter MacCallum Cancer Centre and 11% in the United Kingdom. The PBAC noted that the reasons for this were unclear, but were likely to be related to the amount of tumour cells in the biopsy sample. A greater percentage of cells was required for the dideoxy sequencing test compared to other tests, so retesting may be required at greater cost. If the initial sample was inadequate, a new sample may be required at both greater cost and risk of harm to the patient. Additional samples may also be required if new EGFR mutations were encountered in the tumour, or resistance had developed due to prior radiation exposure. The PBAC considered that these concerns further suggested that the submission's cost-effectiveness estimates favoured first-line gefitinib.

A final concern in relation to testing was the estimated unit cost. The submission estimated a cost based on a range provided by two sources, which differed from that estimated by the Medicare Financing and Analysis Branch of the Department of Health and Ageing.

The submission presented a modelled economic evaluation of advanced/metastatic NSCLC. The 5-year Markov model was based on Weibull regressions for progression and early survival results derived from the EGFR M+ subgroup of the IPASS trial, and results were presented using both deterministic and probabilistic approaches. Given the nature of the disease, this time horizon captured the remaining lifetime of most patients. The model compared first-line therapies (gefitinib or platinum doublet chemotherapy) followed by second-line treatment, assuming that, post-progression, patients initially treated with gefitinib receive platinum-based chemotherapy, and patients initially treated with chemotherapy received gefitinib.

The PBAC recalled that the claim of any overall survival advantage was not supported by the more mature data provided with the pre-subcommittee response. Other assumptions favouring first-line gefitinib were (a) the duration of second-line gefitinib as a cost offset (713 days in the base case based on IPASS compared with 405 days based on utilisation data from Medicare Australia), (b) the assumption that all second-line therapy after doublet therapy is gefitinib, and (c) all patients receiving doublet therapy received second-line therapy. This last assumption was acknowledged as an unintended error in the pre-subcommittee response and the corrected incremental cost per extra quality-adjusted life-year (QALY) gained was estimated to be in the range $75,000 - $105,000 using the deterministic model compared with the original estimate in the range of $15,000 - $45,000 in the submission. The PBAC noted that this corrected ratio was still favourable to first-line

gefitinib for all the reasons it had already identified. For example, increasing the unit cost per test from $400 to $606 increased this ratio to be in the range of $105,000 - $200,000.

The PBAC considered that the estimates of financial implications to the government for both the PBS and the MBS (less than $10 million in the fifth year of listing) were likely underestimates because of the sensitivity of these estimates to the prevalence of EGFR M+ in NSCLC. The PBAC considered the estimate of 9.5% may be an overestimate which was most affected by uncertainties regarding the prevalence in non-Asians and the proportion of Asians in the Australian population.

The PBAC therefore rejected the submission on the basis of unacceptably high and uncertain cost-effectiveness. The main uncertainties related to the prevalence of EGFR M+ in unselected Australian NSCLC patients, EGFR testing performance and cost, the effect of these on the comparative treatment effect of first-line gefitinib, and the extent of the incremental QALY gain based on quality of life advantages without any overall survival advantage.

Recommendation:
Reject

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

AstraZeneca commit to continue working with both the PBAC and MSAC to ensure Australian patients with non-small cell lung cancer are able to identify and access the most effective and appropriate treatments for their disease.