Public Summary Document

Product: Gefitinib, tablet, 250mg, Iressa®
Sponsor: AstraZeneca Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested extension of the current Authority Required listing for gefitinib to include first-line treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) in patients expressing activating mutations of the epidermal growth factor receptor (EGFR) gene.

2. Background

This was the third consideration by the PBAC of gefitinib 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 the Medical Services Advisory Committee (MSAC) consideration.

At its November 2010 meeting, the PBAC rejected a submission seeking a first-line listing for gefitinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (Stage IIIB/IV NSCLC) who have an activating mutation in the epidermal growth factor receptor gene (EGFR M+), 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 (OS) advantage.

At its November 2012 meeting, the PBAC considered a re-submission to extend the current Authority required PBS listing to include first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The co-dependent integrated submission also sought an extension of MBS listing of EGFR mutation testing from MSAC.

The PBAC rejected the re-submission to extend the listing of gefitinib (at the proposed reduced price) to the first-line setting of locally advanced or metastatic NSCLC on the grounds of unacceptably high and uncertain cost-effectiveness. The PBAC also noted the expected lack of any OS gain for patients resulting from the proposed extended listing and that there was insufficient confidence in the accuracy of EGFR test results.

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

For details of previous PBAC consideration for gefitinib, refer to the November 2010 and November 2012 Public Summary Documents (PSDs) available at :
http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd

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 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 (Stage IIIB/ IV) non-small cell lung cancer (NSCLC) in patients with:

(1) a WHO performance status of 2 or less and a diagnosis of non-squamous NSCLC; and

(2) where there is evidence that tumour material harbours an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs).

Authority required

Continuing PBS-subsidised treatment of a patient with locally advanced or metastatic NSCLC who has previously received PBS-subsidised treatment with gefitinib and who does not have progressive disease and who remains on first-line therapy.

The PBAC advised the restriction for gefitinib 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 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 first-line listing be in addition to the current second-line listing.

Consistent with its previous assessment of gefitinib (November 2012 PBAC meeting) the PBAC advised that the proposed gefitinib restriction would need to replace the existing gefitinib restriction. Further, PBAC considered that the restriction should not specify the line of therapy for use of gefitinib in EGFR mutation positive patients. Thus, review and

alignment of the current restriction for TKIs will allow clinicians to use TKIs for EGFR mutation positive NSCLC as first or later line therapy. The PBAC considered that patients with EGFR wild type (M-) NSCLC should not be exposed to TKIs because of the negative impact of these drugs, particularly when used in place of effective chemotherapy. The PBAC also noted the applicant's position that treatment of EGFR M- patients with an EGFR TKI was inappropriate.

5. Clinical Place for the Proposed Therapy

The re-submission proposed that the place in therapy of gefitinib is to replace platinum-based doublet chemotherapy as the first-line treatment of locally advanced or metastatic NSCLC in patients with evidence of activating EGFR mutations. This is as previously accepted by the PBAC.

6. Comparator

The re-submission nominated platinum-based doublet chemotherapy with carboplatin and paclitaxel as the appropriate main comparator.

The PBAC accepted the comparator is platinum doublet chemotherapy, and noted that while there were likely to be some differences in efficacy of different doublets (e.g. pemetrexed doublets are more effective than gemcitabine or paclitaxel doublets in non-squamous NSCLC), on balance, for the purposes of the current re-submission, the PBAC accepted these doublets are clinically non-inferior to each other.

The PBAC also considered that erlotinib and afatinib were relevant comparators.

7. Clinical Trials

The re-submission presented four randomised trials:

- two trials, IPASS (the key trial) and First-SIGNAL, compared gefitinib with platinum-based chemotherapy in unselected NSCLC patients; and
- two trials (NEJ002 and WJTOG3405) comparing gefitinib with platinum-based chemotherapy in EGFR mutation positive (M+) NSCLC patients.

These trials were unchanged from the November 2012 re-submission.

The IPASS and First-SIGNAL trials provided data on the effectiveness of first-line gefitinib relative to first-line platinum-based doublet chemotherapy (carboplatin + paclitaxel and cisplatin + gemcitabine, respectively) in patients with locally advanced or metastatic NSCLC. Cross over to second-line therapy after disease progression was allowed, and broadly reflects current practice for the group randomised to platinum-based doublet chemotherapy. Retrospective analysis of EGFR mutation status of patients with evaluable tumour samples allowed effectiveness to be compared in different population groups: a) the intention-to-treat (ITT) study population, b) patients with an EGFR mutation positive, c) patients with wild-type EGFR status (M-), and d) patients who provided no evaluable tumour samples and had an unknown EGFR mutation status. All patients included in the other two controlled trials, (NEJ002 and WJTOG3405) had advanced or metastatic EGFR mutation positive NSCLC.

For details of the published trials presented in the submission, refer to the November 2012 gefitinib PSD.

8. Results of Trials

The PBAC accepted that first-line gefitinib therapy is more effective than first-line platinum-based doublet chemotherapy in patients with EGFR M+ NSCLC in terms of prolonged progression-free survival (PFS). For example, in the IPASS trial, the mean PFS was 9.5 months, compared to 6.3 months in the control group (median increase in PFS of 3.2 months, HR=0.48 95% CI: 0.36, 0.64) for patients with EGFR M+ tumours. There was however no difference in overall survival (OS) between the two groups. On the other hand, in patients with wild type EGFR (M-) NSCLC, first-line gefitinib was significantly less effective in terms of PFS compared with first-line platinum-based doublet chemotherapy (PFS 1.5 months with gefitinib compared to 5.5 months with chemotherapy). Overall survival as also quantitatively less in the gefitinib arm (median 11.2 months) compared with the chemotherapy arm (12.7 months). This establishes the need for EGFR testing before deciding whether to use gefitinib and also establishes the importance of minimising false positive EGFR test results (improving the specificity of an EGFR test).

The OS data were updated for trials NEJ002 and WJTOG3405, but were still immature for the WJTOG3405 trial. As seen in the IPASS and First-SIGNAL trials, there was no significant difference between the two treatment arms in terms of OS (NEJ002 HR=0.89; 95% CI: 0.63, 1.24; WJTOG3405: HR=1.19; 95% CI: 0.77, 1.83).

While there was no significant survival advantage reported for gefitinib in comparison with platinum-based doublet chemotherapy, the survival analysis might be confounded by cross over. The PBAC considered that given the large number of patients who received a second line TKI in the trials reflects current PBS practice, the data suggest that TKIs could be available for EGFR M+ patients either as first line treatment or as second-line following doublet chemotherapy and would achieve similar clinical outcomes.

The PBAC considered that it is difficult to conclude whether gefitinib is non-inferior in terms of effectiveness compared to erlotinib or afatinib based on the indirect comparisons presented across the three 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 gefitinib, erlotinib and afatinib are likely to be clinically non-inferior to each other and the decision as to which TKI to use should be left to the prescribing clinician. 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 gefitinib 250 mg daily, erlotinib 150 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.

With regard to comparative harms, no new safety data were presented in the current re-submission. The toxicity data from the November 2012 co-dependent re-submission demonstrated that the most common adverse events reported in the four gefitinib trials were

consistent with the known safety profile of the treatments. Overall, safety profiles varied across the treatment arms, but gefitinib appeared to have less serious toxicity than platinum-based therapy.

The PBAC agreed that the TKIs have slightly different toxicity profiles (e.g. treatment with afatinib may cause 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 in clinical practice toxicity is managed by dose reductions rather than switching to another TKI. This was also the conclusion from the EGFR/TKI stakeholder meeting.

9. Clinical Claim

The re-submission described first-line gefitinib treatment of patients with EGFR M+ NSCLC as superior in terms of PFS and non-inferior in terms of OS when compared with platinum-based doublet chemotherapy. The re-submission described gefitinib as superior in terms of comparative safety over platinum-based doublet chemotherapy.

As previously, the PBAC accepted that the clinical benefit of listing gefitinib in patients with EGFR M+ NSCLC as first-line treatment in addition to the current listing for second-line treatment is an improvement in quality of life, but not a prolongation of life. The PBAC accepted that gefitinib appears to have less serious toxicity than platinum-based doublet chemotherapy.

The PBAC agreed that, on balance, gefitinib is likely to be non-inferior compared to erlotinib or afatinib and the choice of TKI for use in an individual patient should be left to the clinician.

10. Economic Analysis

The re-submission presented an updated modelled economic evaluation: a cost-utility analysis in terms of cost per quality-adjusted life-year (QALY) gained based on a superiority claim of the proposed scenario (both EGFR testing with NSCLC diagnosis and first-line gefitinib are available) over the current scenario (neither EGFR testing with NSCLC diagnosis nor first-line gefitinib is available) for both comparative benefit and harms. Given there is no apparent OS benefit from first line gefitinib treatment of EGFR M+ NSCLC, the additional QALYs gained in the proposed scenario rest on utility gains from delaying progression, deferring utility decrements in later health states, and the improved quality of life (QoL) associated with gefitinib treatment (oral administration, less serious toxicity), as opposed to doublet chemotherapy.

The re-submission claimed dominance of first-line gefitinib in terms of incremental costs and QALYs gained over treatment with carboplatin + paclitaxel, based on the IPASS trial, extrapolated to 5 years (from a median follow-up of 17 months in the trial). Utility values were applied from QoL scores reported in the IPASS trial after being converted using an algorithm derived from another TKI (second-line) clinical trial (ZODIAC), as well as utility decrements associated with disease progression reported in one published study (Nafees et al 2008).

The PBAC noted the economic model is based on the proposed first-line gefitinib price which is reduced from the current gefitinib price for second-line therapy. The sponsor did not propose a final price weighted across the two lines of therapy.

The result of the economic analysis shows that, in the base case, first-line gefitinib delivers a benefit of 0.0152 QALY (i.e. ~5 days of perfect health) and a cost saving; that is, gefitinib is dominant at the proposed price. The small incremental costs and small incremental benefits make the incremental cost effectiveness ratio extremely volatile. Depending upon the various assumptions in the model, the PBAC noted the incremental cost-effectiveness ratio (ICER) could range from dominant to $45,000 - $75000/QALY.

For example, as shown in the univariate sensitivity analyses presented in the submission and conducted during the evaluation, by varying only one assumption, the proportion of patients going on to second-line treatment, the ratio changes from dominant in the base case to $15,000 - $45,000/QALY if the proportion reduces to 44%, and to -($45,000 - $75,000)/QALY if the proportion increases to 80%.

The claim of dominance is due primarily to the cost offsets associated with second-line gefitinib. This is because the price of second line gefitinib is twice the proposed price of first-line gefitinib and the comparator arm of the model assumes 60% of EGFR M+ patients who are alive after disease progression will move on to second-line therapy with gefitinib. To further consider the impact of the cost of second line TKIs on the ICER, the PBAC used the price of erlotinib (which is not in the public domain) in the model. This analysis demonstrated that the revised ICER for gefitinib is estimated to be in the upper range of $45,000 - $75,000/QALY. The incremental cost-effectiveness ratios have been expressed as a range to ensure consistency with the practice adopted by Public Summary Documents.

The PBAC also considered that the claim of 60% uptake of second-line gefitinib in the comparator arm is a likely overestimate. When IPASS and Medicare utilisation data are considered together, the estimate for second-line uptake of gefitinib is considerably less. IPASS results showed that second-line TKI accounted for 61% (43/71) of all active second-line therapies in the comparator arm (first-line carboplatin/paclitaxel arm), with the remaining being different chemotherapy regimens. However, Medicare data suggested that only 62% (44/70) of patients who were alive at the end of first-line treatment received any second drug, which included switch maintenance therapy or any active second-line treatment.

Another driver of the model is the specificity of EGFR testing. The base case economic analysis assumes 100% accuracy of EGFR testing. However, a lower specificity of an EGFR test (i.e. classifying patients M+ who are in fact M-) has important clinical implications because the PFS is much reduced in a patient with a false positive result who should have received chemotherapy, but is instead treated with a TKI. The impact of the test's performance on the ICER has been tested in sensitivity analyses conducted in the submission and during the evaluation.

Overall, the PBAC agreed with the Economic Sub-Committee (ESC) that the base case ICER was biased in favour of gefitinib. Factors contributing to this bias were the:

- assumption that a high proportion of patients in the comparator arm moving on to second-line gefitinib;

- failure to take into account the use of second-line erlotinib in Australian clinical practice;
- underestimates of the cost of re-biopsy; and
- overestimates of the costs for management of chemotherapy-associated adverse events.

The PBAC also noted the ESC advice that the ICER would move from dominant in the base case to dominated if gefitinib delivers a survival benefit. The ICER was calculated as less than $15,000 /QALY for both 3 months survival benefit and 6 months survival benefit. The reason the ICER increased under the assumption of survival benefit related to the longer duration of the post-progression period and the costs incurred in this period. These additional costs relate to the longer duration of later-line therapies in the gefitinib arm which alters the cost difference between the gefitinib and comparator arm from negative (cost saving) to positive.

The PBAC noted that maintenance therapy with pemetrexed (not explicitly excluded by the restriction) or erlotinib (explicitly excluded by the restriction) is used in clinical practice, but it has not been considered by PBAC and its cost effectiveness is unknown. The PBAC noted that the gefitinib model appropriately does not include a maintenance therapy option in the base case economic analysis.

For reasons outlined above, the PBAC concluded that the submission's claim of dominance of first-line gefitinib over doublet chemotherapy in terms of incremental costs and QALYs is highly uncertain.

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 Government in the range of $10 - $30 million in Year 5.

The Drug Utilisation Sub-Committee (DUSC) considered that the total number of non-squamous or not otherwise specified NSCLC EFGR mutation positive patients provided a theoretical upper limit on utilisation.

The PBAC noted the DUSC advice regarding the likely total number of EGFR mutation positive patients in the first five years of listing and that that the biggest potential for increased utilisation of gefitinib is if the prevalence of EGFR M+ is higher than expected. The DUSC acknowledged that 15% (range is 10% to 20%) is appropriate for the base case based on MSAC advice.

The re-submission's estimate of prescriptions/year and cost/year for gefitinib assumed a 100% uptake rate in eligible patients and estimated the mean number of gefitinib prescriptions for first line treatment based on the PFS result from the IPASS trial (10 prescriptions per patient for first-line gefitinib; median PFS in EGFR M+ patients receiving gefitinib: 9.5 months versus 7 prescription per patient for second-line gefitinib, based on the INTEREST trial). The current gefitinib second-line patient co-payment split is used to estimate the patient co-payment associated with first-line gefitinib.

The re-submission estimated a saving to the PBS for chemotherapy of less than $10 million (revised) in Year 5, assuming that if gefitinib is listed on the PBS for first-line treatment of NSCLC, it would substitute for first-line platinum-based doublet chemotherapy and alter the use of second-line treatment in the target population. The DUSC did not consider that cost offsets for second line gefitinib are realistic as:

- Patients are likely to continue on a TKI in second line, and
- If gefitinib is used in combination with chemotherapy as initial treatment rather than as monotherapy as specified in the restriction the cost offsets will not eventuate.

The financial implications are to be further verified.

The PBACnoted the DUSC's advice that the estimated cost to the MBS is an underestimate as it does not include:

- costs to the MBS for EGFR re-testing,
- costs to the MBS for re-biopsy and for management of biopsy complications for patients treated in a public hospital as private patients or in a private hospital, and
- costs to the MBS for managing adverse events from NSCLC therapies.

The PBAC noted the differences 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 agreed with the DUSC that the biggest financial risk is the duration of first-line therapy as it is common for targeted therapies to be continued after progression, which would not be in accordance with the proposed PBS restriction for gefitinib.

The sponsor stated its awareness of the requirement for listings that may result in net costs to the PBS greater than or equal to $10 million in the first year of listing to enter into a Risk Share Agreement (RSA), but also stated that if more than one TKI is listed for this indication, the threshold would not be reached and a RSA would not be necessary.

The PBAC considered that a risk share agreement would be needed to ensure that gefitinib was not subsidised for use beyond disease progression. The PBAC re-iterated that PBS use of gefitinib should be available for all EGFR M+ positive tumours. Because much of the data regarding the efficacy of the TKIs had been determined for patients with the common activating mutations (i.e. L858R at exon 21 and exon 19 deletions) PBAC considered post-marketing monitoring of both EGFR testing and TKI utilisation was required. This strategy will allow evidence to evolve for patients with rare mutations in EGFR. The RSA could address the need for appropriate data collection and potential for a different efficacy or safety profile in rare EGFR activating mutations.

12. Recommendation and Reasons

The PBAC advised that the existing gefitinib restriction should be replaced by the proposed gefitinib restriction so that no line of therapy is specified.

The PBAC accepted that the comparator for gefitinib and the other two tyrosine kinase inhibitors (TKIs) considered at the July 2013 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 gefitinib and the other two TKIs are more effective than platinum-based doublet chemotherapy in patients with EGFR mutation positive NSCLC in terms of improving 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 gefitinib 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 for patients with EGFR M+ NSCLC in the as first-line setting or following doublet chemotherapy. In other words, the data indicate there is no difference in progression-free survival or overall survival whether a TKI is given as first-line or second-line therapy to patients with EGFR M+ 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 of the three TKIs involving 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 likely to be 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.

The gefitinib re-submission presented an updated modelled economic evaluation based on the superiority claim of the proposed scenario (EGFR testing performed contemporaneously with a diagnosis NSCLC and availability of first-line gefitinib) compared with the current scenario (neither EGFR testing nor first-line gefitinib is available). As previously, concluded there was a lack of evidence for an additional benefit of first line treatment with TKIs in terms of overall survival. The benefits of gefitinib as first-line treatment for patients with EGFR M+ positive NSCLC compared with doublet chemotherapy therefore rely on the utility gains in the PFS state, deferral of utility decrements in later health states, and the improved quality of

life (QoL) associated with gefitinib treatment (oral administration, less serious toxicity), as opposed to doublet chemotherapy.

The result shows that, in the base case, first-line gefitinib delivers a benefit of 0.0152/QALY and a cost saving, that is, gefitinib is dominant at the proposed price. The small incremental costs and small incremental benefits make the ratio extremely unstable. This is reflected in analyses that show gefinitib is either dominant or dominated depending on underlying assumptions.

The claim of dominance is due primarily to the cost offsets associated with second-line gefitinib in the comparator arm. First line gefitinib would no longer be a dominant treatment over doublet chemotherapy if erlotinib is used in second-line rather than gefitinib. Using the price of erlotinib, which is not publicly available, and consistent with the practice adopted by Public Summary Documents to express incremental cost-effectiveness ratios, the revised incremental cost effectiveness ratio is estimated to be towards the upper range of $45,000 - $75,000/QALY. The economic analysis also showed that the ICER was sensitive to the proposed 60% rate of uptake of second-line gefitinib in the comparator arm. The data showed that 60% was an overestimate of uptake rates.

Further, the PBAC noted the ESC advised of a series of other concerns with the model that bias it in favour of gefitinib, namely that the model:

- assumes a high proportion of patients in the comparator arm moving on to second-line gefitinib;
- does not take into account the use of second-line erlotinib in Australian clinical practice;
- underestimates the cost of re-biopsy; and
- overestimates the costs for management of chemotherapy-associated adverse events.

Overall, the PBAC concluded that, at the price proposed, the economic analysis suggests that the cost-effectiveness of gefitinib is uncertain and more likely to be in the upper range of $45,000 - $75,000/QALY rather than dominant. Given the small QALY difference between the two arms of the economic model, small alterations in some inputs, such as the uptake rate of second-line doublet chemotherapy/gefitinib and the cost for second-line TKI therapy have a large impact upon the estimated incremental cost-effectiveness ratio.

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 gefitinib 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 individuals and health care professionals via the Consumer Comments facility on the PBS website. Most notably, comments cited improvement in quality of life, less hospital visits for I.V chemotherapy, less toxicity and superior control of symptoms as benefits associated with treatment with gefitinib.

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

The PBAC proposed that a price reduction would be the most expeditious way of arriving at an acceptable basis to recommend the listing of gefitinib. This would support PBAC's intention of ensuring better use of all TKIs, including by reducing the use of those TKIs which as currently listed are not cost-effective. This proposal also 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 rebating to an effective price.

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

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
GEFITINIB Tablet 250 mg	30	3	Iressa® AstraZeneca Australia Pty Ltd

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

Clinical criteria:	The condition must be non-squamous, **OR** The condition must be not otherwise specified (NOS); **AND** The treatment must be as monotherapy Patient must not have received prior treatment with a tyrosine kinase inhibitor (TKI) for this condition, **OR** Patient must have developed intolerance to another TKI of a severity necessitating permanent treatment withdrawal; **AND** Patient must have a WHO performance status of 2 or less. **AND** Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with TKIs in tumour material.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
GEFITINIB				
Tablet 250 mg	30	3	Iressa®	AstraZeneca Australia Pty Ltd

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
Clinical criteria:	The treatment must be as monotherapy **AND** Patient must have previously been issued with an authority prescription for this drug **AND** Patient must not have progressive disease.

Outcome:
Defer

Subsequent to the meeting, the sponsor offered to further reduce gefitinib's price.

The price offer was derived from a revised incremental cost-effectiveness ratio of $15,000 - $45,000 per QALY gained (without maintenance). The new ratio was calculated by varying two key variables of the economic analysis:

a) the proportion of patients in the comparator arm moving on to second-line gefitinib from 60% in the base case to 50%. The sponsor considered that a 44% estimate used in a sensitivity analysis conducted during the evaluation was too low.

b) second line treatment gefitinib as well as erlotinib, which has a lower price, in the comparator arm of the economic model. Given that erlotinib has a Special Pricing Agreement, the sponsor assumed that the price of erlotinib is lower than the price of gefitinib, and that gefinitib and erlotinib are equally used.

The sponsor did not make further revisions to the costs of re-biopsy, or the costs of managing chemotherapy-associated adverse events, from what was presented in the base-case economic analysis.

The PBAC recommended the listing of gefitinib, on an Authority Required basis as discussed below. However, in light of PBAC's out-of-session recommendation for the PBS-listing of erlotinib at an effective price lower than the price offered from gefitinib, and the PBAC's previous conclusion that the erlotinib and gefitinib are likely to be clinically non-inferior to each other, the PBAC considered that gefitinib would not be cost-effective under the sponsor's pricing proposal.

The PBAC considered that the cost-effectiveness of gefitinib would be acceptable if gefitinib was cost-minimised against erlotinib, and if a risk-share arrangement was negotiated with the sponsor of gefitinib which satisfactorily addresses risks of excessive utilisation and use in patients with rare EGFR activating mutations. Information regarding usage will inform decisions regarding rebating to an effective price.

The listing would be 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. Gefitinib is to cease on disease progression.

The equi-effective doses, based on doses from trials, are gefitinib 250mg daily and erlotinib 150mg daily.

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

The sponsor has no comment.