Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1293 – Epidermal Growth Factor Receptor (EGFR) testing to determine eligibility for afatinib treatment in patients with locally advanced or metastatic non-small-cell lung cancer

Sponsor/Applicant/s: **Boehringer Ingelheim Pty Limited**

Date of MSAC consideration: **1 August 2013**

1. Purpose of application

In February 2013, the Department of Health and Ageing received an application from Boehringer Ingelheim Pty Limited requesting Medicare Benefits Schedule (MBS) listing of epidermal growth factor receptor (EGFR) mutation testing for non-squamous (or not otherwise specified) non-small-cell lung cancer (NSCLC) to determine eligibility for first-line treatment with afatinib, through the Pharmaceutical Benefits Schedule (PBS).

The proposed intervention is a genetic pathology test aimed at detecting somatic EGFR mutations in NSCLC tumour tissue. The sub-group of NSCLC tumours that harbour an EGFR "activating" mutation have increased phosphorylation of EGFR and consequently an over-activated intracellular kinase pathway; this increased downstream signalling leads to cell proliferation and contributes to the malignant phenotype in these patients. Most of these mutations occur between exons 18 and 21 of the tyrosine kinase activation domain and result in ligand overexpression. Currently, 80-90% of all mutations identified are either exon 19 in-frame deletion and/or insertion mutations or an exon 21 missense mutation (L858R - causing a leucine to arginine substitution) (Gately et al 2012; Sharma et al 2007).

At the October 2012 MSAC/PBAC stakeholder meeting, it was considered that a more appropriate ratio for common to rare mutations was70%:30% because the accuracy and sensitivity of testing methodologies will most likely improve in the future. As a consequence, a greater proportion of patients with NSCLC containing rare EGFR mutations would be expected to be identified.

EGFR mutation testing of NSCLC tumour cells will enable the identification of patients who may benefit from targeted drug therapy. EGFR tyrosine kinase inhibitors, such as afatinib, bind at the ATP site of the ligand and inhibit phosphorylation and receptor signalling. This enables restoration of normal downstream cellular processes such as apoptosis (cell death), leading to decreased tumour cell proliferation.

Currently, EGFR mutation testing is available on the MBS to patients with locally advanced or metastatic NSCLC to determine eligibility for access to second-line treatment with gefitinib under the PBS.

MSAC proposed that all patients with NSCLC unequivocally shown not to have squamous cell histology at the time of initial diagnosis should be eligible for EGFR mutation testing (irrespective of disease stage).

2. Background

No previous applications for EGFR mutation testing of NSCLC patients to determine eligibility for treatment with afatinib have been submitted to MSAC. However, there have been previous applications related to EGFR testing.

In December 2010, MSAC recommended public funding for 'testing in the limited circumstance of determining tumour EGFR activating mutation status to contribute to a determination of eligibility for currently PBS-subsidised gefitinib for a patient with locally advanced or metastatic non-small cell lung cancer'. EGFR testing for access to gefitinib in the second-line setting has been MBS listed since May 2012.

In October 2012, a Stakeholder Meeting was jointly convened by MSAC and PBAC to resolve outstanding issues related to i) EGFR mutation testing, and ii) the clinical place of tyrosine kinase inhibitors (TKIs) in the treatment of locally advanced (Stage IIIb) or metastatic (Stage IV) NSCLC.

In November 2012, MSAC discussed Application 1161 (EGFR mutation testing for first-line treatment with gefitinib), and taking into account the advice from the Stakeholder Meeting, advised on outstanding EGFR mutation testing issues that needed to be addressed for access to EGFR TKIs as first-line therapy in locally advanced or metastatic non-squamous NSCLC. This was needed as a co-dependent submission to PBAC and MSAC relating to erlotinib – which had previously been PBS listed as later line therapy in an *unselected* NSCLC population – had requested first-line treatment contingent on EGFR mutation status (MSAC Application 1173, considered by MSAC in August 2012).

The applicant was advised to provide a "minor" submission to MSAC to address key information requirements for Application 1293.

3. Prerequisites to implementation of any funding advice

No specific test was requested for MBS listing. The submission noted that testing may require tumour cell enrichment or the use of a method more sensitive than Sanger sequencing. Most EGFR testing is likely to be "in-house" as part of a laboratory network and under the control of an Approved Pathology Authority.

EGFR mutation testing must be performed in National Association of Testing Authorities (NATA) accredited laboratories.

The Royal College of Pathologists of Australasia (RCPA) and Human Genetics Society of Australasia (HGSA) conduct a Molecular Genetics Quality Assurance Program for EGFR mutation screening of human tumours in Australian pathology laboratories.

4. Proposal for public funding

The submission requested a change to the current MBS listing as detailed below. The proposed MBS listing in the Final DAP for application 1293 was modified by the submission to include the underlined sentence.

Current and proposed MBS item descriptor for EGFR mutation testing

Current MBS item descriptor for EGFR mutation testing
Category 6 – Pathology Services Group P7 - Genetics
73328 A test of tumour cells from a patient with locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $397.35; Benefit: 75% = $298.05, 85% = $337.75
Proposed MBS item descriptor for EGFR mutation testing for access to afatinib
73328 A test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer (NSCLC) requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to gefitinib or erlotinib or afatinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Testing should be carried out from the time of initial diagnosis in NSCLC patients unequivocally shown not to have squamous cell histology. Fee: $397.35 Relevant explanatory notes: The test will, ordinarily, be initiated by a pathologist, medical oncologist or respiratory physician (or occasionally a surgeon). Samples with low quality DNA or low tumour cell content relevant to the sample size available and chosen testing method may require tumour cell enrichment or the use of a method more sensitive than Sanger sequencing.

Source: http://www9.health.gov.au//mbs/fullDisplay.cfm?type=item&q=73328&qt=item&criteria=73328, and Table A.4 of main submission to PBAC

Under the proposed MBS item descriptor, EGFR mutation testing would be restricted to patients with non-squamous or not otherwise specified NSCLC. Patients with squamous NSCLC would not be eligible for testing.

The applicant's proposed PBS restriction for afatinib for consideration at the July 2013 PBAC meeting is as follows:

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.

MSAC advice from the November 2012 Minutes for Application 1161 suggested that:

- the proposed MBS item descriptor should require that EGFR testing be performed on the same specimen in the same laboratory as the prerequisite histology testing because this would optimise both confidence in pathology results and parsimonious use of the specimen
  - The submission agreed with MSAC and supported the inclusion of a statement to this effect in the MBS item descriptor.
- the proposed MBS item should therefore be made a pathology determinable service so that the pathologist can proceed to the second EGFR testing step as indicated by the prerequisite histology step without being interrupted to get a referral from a clinician to do so.

- The submission advocated so-called "reflex" testing on suitable (non-squamous NSCLC) specimens once histology results are available. However, this was not currently reflected in the proposed MBS item descriptor.

Changes to pathology services

MSAC advice from the November 2012 minutes for Application 1161 recommended that:

- pathology practice should be optimised to ensure EGFR testing is limited to laboratories with appropriate expertise and back-up through a more centralised approach by requiring that the one laboratory performs both the histology and genetic testing on the specimen
- this centralised approach should also be developed to facilitate the collation of data across standardised reports to the requesting oncologists on the prevalence of various types of detected EGFR mutations and the clinical basis for determining whether they predict sensitivity or resistance to subsequent TKI therapy
- biopsy sampling practice should also be optimised to obtain sufficient tumour tissue of adequate quality to obtain high rates of satisfactory specimens.

The submission supported:

- processes optimising pathology practice standards and limiting public subsidy for EGFR testing to suitably accredited laboratories who can perform both the histology and genetic testing (EGFR mutation testing) on the specimen
- a centralised approach to the collection of data on the prevalence of the various different EGFR mutations and the clinical basis for predicting sensitivity or resistance to EGFR TKI therapy
  - however, the sponsor was unclear as to what, if any, role it would play in the establishment and maintenance of such services
- optimisation of biopsy sampling practices to ensure the best quality and quantity of tumour specimens are available for testing to minimise re-biopsy rates
- educational initiatives on this theme in the past, for example a Symposium at the 2012 Thoracic Society ANZ Meeting.

5. Consumer Impact Statement

PASC received 3 individual responses during the public consultation period for the DAP: 2 from professional bodies (The Royal College of Pathologists of Australasia and The Medical Oncology group of Australasia) and 1 from a consumer group (Cancer Voices Australia). The concerns raised included: the prevalence of EGFR mutations, when to test, reflex testing, and what to test (common or uncommon mutations). These issues were all raised in the October 2012 MSAC/PBAC Stakeholder Meeting on EGFR mutation testing, and in the November 2012 MSAC meeting to discuss Application 1161 (EGFR mutation testing for first-line treatment with gefitinib).

6. Proposed intervention's place in clinical management

EGFR mutation testing would be used to identify a subgroup of patients with non-squamous NSCLC who would likely benefit from treatment with afatinib once they have progressed to locally advanced or metastatic disease.

EGFR mutation testing for access to first-line TKIs will result in some additional testing because currently testing should only occur in patients who have stage IIIb/IV NSCLC so that they can access gefitinib as a second-line treatment option. However, as most people progress to advanced disease within 2 years, the number of additional tests performed will be small. Thus, the proposed intervention will mostly change the timing of the test (relative to treatment) for those patients diagnosed with an earlier stage of disease.

All patients diagnosed with, or progressed to, stage IIIb/IV NSCLC would then be treated according to the results of the EGFR mutation test. Those with an activating mutation of the EGFR gene would be eligible to receive afatinib, while those who do not have an EGFR mutation would receive platinum doublet chemotherapy.

Prevalence of EGFR mutations in NSCLC

The base case scenario of the economic evaluation and financial analysis in the submission used 16% for the prevalence of activating EGFR mutations and examined a range of 12% to 20% in the sensitivity analysis. This is similar to the prevalence of 15% with a range of 10% to 20% for sensitivity analysis that MSAC recommended should be presented to PBAC in the November 2012 Minutes for Application 1161 and does not substantially affect the economic evaluation.

7. Other options for MSAC consideration

Whom to test

The November 2012 MSAC advice for Application 1161 suggested that the proposed MBS item descriptor should exclude EGFR testing from patients with NSCLC tumours shown unequivocally to have squamous cell histology.

- The submission agreed with MSAC as it is consistent with international consensus guidelines on EGFR testing and with the available epidemiological evidence on the frequency of EGFR mutations in the squamous cell subtype, which is extremely low.
- However, the wording of the proposed listing could be confusing:
  - initially, the wording does not specify squamous or non-squamous cell histology, suggesting the testing of "tumour cells from a patient with locally advanced or metastatic NSCLC"
  - however, the following sentence then states that "Testing should be carried out from the time of initial diagnosis in NSCLC patients unequivocally shown not to have squamous cell histology" and
  - this could be misinterpreted to allow testing of patients with squamous cell NSCLC who have progressed to locally advanced or metastatic disease.

What to test

Taking into account the October 2012 Stakeholder Meeting advice, MSAC considered that the definition of the biomarker in a PBS restriction should be any EGFR activating mutation, rather than being limited to exon 19 deletions and exon 21 L858R point deletions only (as suggested by PBAC in the context of its November 2010 consideration of first-line gefitinib in the same patient population).

- The submission agreed with MSAC with respect to the definition of a positive EGFR mutation test.

The November 2012 MSAC advice for Application 1161 advised that the corresponding economic evaluation presented to PBAC should reflect the fact that the common mutations (exon 19 deletions and exon 21 L858R point mutations) comprise only 70% of all activating mutations and that the effectiveness of gefitinib has only been demonstrated in randomised trial evidence for these mutations.

- The submission disagreed that the common mutations comprised only 70% of EGFR activating mutations. In the LUX Lung 3 trial almost 90% of enrolled patients had these mutations.

When to test

The November 2012 MSAC advice for Application 1161 suggested that the descriptor should allow NSCLC patients to have EGFR testing from the point of initial diagnosis of NSCLC.

- This advice was based on the following:
  - only a minority of early stage non-squamous NSCLC cases will not eventually relapse, consequently there would be no unnecessary EGFR testing following this approach and
  - a small but favourable advantage in cost/QALY can be gained for testing at diagnosis, mainly by avoiding costs of retrieving FFPE tissue blocks from archive in approximately 40% of patients diagnosed prior to development of Stage IIIb/IV NSCLC.
- The submission agreed with the MSAC view that testing at diagnosis would be appropriate, but considered that the wording of the proposed listing for afatinib is confusing:
  - initially, the wording advocates testing of tumour cells "from a patient with locally advanced or metastatic NSCLC", but
  - the following sentence then states that "Testing should be carried out from the time of initial diagnosis".
- The submission to PBAC presented an alternative scenario to the base case analysis in the economic evaluation where testing is conducted on progression to Stage IIIb/IV disease.

Prevalence of EGFR mutations in early versus late stage NSCLC

MSAC noted several studies which compared the prevalence of EGFR mutations in early versus late stage NSCLC disease at diagnosis. Overall, there was very little difference in the prevalence of EGFR mutations at diagnosis of early and late stage disease with a median 17.8% in early stage (I-IIIa) and 15.4% in late stage (IIIb-IV) NSCLC.

The October 2012 Stakeholder Meeting minutes stated that repeat testing for EGFR mutations would not be required for checking multiple sites to confirm concordance of EGFR status or for assessing mutation stability over time.

Treatment algorithm in economic model compared to final DAP

The treatment sequences used in the economic model are consistent with those presented in the final DAP, with exception of the inclusion of a sequence where second-line afatinib is modelled in EGFR mutation positive patients after first-line treatment with erlotinib or gefitinib. This sequence was modelled for the majority of patients treated with a first-line TKI.

8. Comparator to the proposed intervention

The comparator to EGFR mutation testing in the current treatment pathway for locally advanced or metastatic non-squamous NSCLC is 'no testing' in both the Final DAP and the submission.

The November 2012 MSAC advice for Application 1161 agreed that the nominated comparator of no EGFR testing was appropriate. Also in line with MSAC Advice, the proposed management algorithm allows for EGFR mutation testing of all patients with non-squamous NSCLC, at initial diagnosis.

In the current scenario of 'no testing', platinum-based doublet chemotherapy (mostly carboplatin + gemcitabine) is the preferred treatment offered to patients with locally advanced and metastatic NSCLC as a first-line therapy. Under the proposed intervention, EGFR mutation testing of patients with non-squamous NSCLC will enable the use of afatinib as a first-line therapy for those who are EGFR mutation positive on diagnosis of, or progression to, stage IIIb or stage IV disease.

Although the submission proposed that the main comparator for afatinib treatment is platinum doublet chemotherapy, it is possible that EGFR mutation testing for access to first-line erlotinib and/or gefitinib may be potential future comparators. Therefore, these possible alternatives were included in the DAP decision analysis and the submission addressed them to inform MSAC and PBAC.

9. Comparative safety

The main safety concern with EGFR testing is the need to re-biopsy in order to attain a testing sample of sufficient size. Re-biopsy can result in complications such as pneumothorax and haemorrhage, which were considered to occur in 12.6% and 1.4% of re-biopsy cases, respectively.

The October 2012 Stakeholder Meeting minutes considered that repeat testing for EGFR mutations would only occur in unusual and specific circumstances, as repeat testing was not needed for monitoring purposes; assessing the development of resistance; checking multiple sites to confirm concordance of EGFR status; assessing mutation stability over time or in response to various treatments; or re-establishing eligibility for another TKI. However, there is some evidence to suggest that repeat testing after exposure to cancer therapies may be beneficial for those patients whose EGFR mutation status changes.

Some patients would need to be re-biopsied and retested due to either an insufficient tumour sample or an inconclusive EGFR mutation test result. MSAC Advice from the November 2012 Minutes for Application 1161 recommended that the economic evaluations and financial analyses presented to PBAC should include a re-biopsy rate of 12% to reflect the rate of indeterminate results from the initial biopsy.

This has been taken into account in the economic evaluation and financial analyses presented to PBAC by the sponsor, with a re-biopsy rate of 8.7% (taken from the LUX Lung 3 trial, which used the TheraScreen EGFR mutation testing method), with sensitivity analysis using 15% and 30% to reflect the use of real-time PCR mutation detection kits and direct DNA sequencing methods commonly used in Australian pathology laboratories. This base rate is lower than the recommended 12% re-biopsy rate suggested by MSAC, however it is acknowledged that, with increasing experience and knowledge of sampling requirements, the re-biopsy rate may decrease over time.

10. Comparative effectiveness

There is no accepted ‘reference standard’ against which the performance of EGFR mutation testing methods can be compared. Thus, MSAC considered a comparison of analytical performance of the alternative test options to be appropriate. However, the only requirement relating to test performance for this minor submission to MSAC was to provide a detailed description of the testing strategy (the “evidentiary standard”) used in the trials presented in the submission to PBAC.

The submission provided details of the methods used in the main EGFR TKI clinical trials and in Australian laboratories: a summary of these methods is shown in the table below.

Summary of EGFR mutation testing methods used in clinical trials and Australian pathology laboratories

Drug	Clinical Trial	EGFR mutation testing method
Afatinib	LUX Lung 3	DxS TheraScreen® EGFR 29 Mutation Detection Kit (uses Scorpion-ARMS technology)
Erlotinib	EURTAC	DNA sequencing, fragment length analysis (exon 19), TaqMan assay (exon 21)
Erlotinib	OPTIMAL	DNA sequencing, fragment length analysis (exon 19), Cycleave assay (exon 21)
Gefitinib	IPASS	DxS TheraScreen® EGFR 29 Mutation Detection Kit (uses Scorpion-ARMS technology)
Gefitinib	First-SIGNAL	DNA sequencing of exons 19, 20 and 21 (repeated to confirm)
Gefitinib	NEJ002	PNA-LNA PCR clamp
Gefitinib	WJOTG3405	Fragment length analysis (exon 19), Cycleave assay (exon 21) confirmed by DNA sequencing

Australian pathology laboratories	Direct DNA sequencing Mass Spectrometry Sequenom Scorpion ARMS technology (including DxS TheraScreen® Kit) TaqMan® Mutation Detection Assays Cobas® EGFR Mutation Test

ARMS = Amplified Refractory Mutation System; EGFR = epidermal growth factor receptor; PCR = polymerase chain reaction; PNA-LNA = peptide nucleic acid-locked nucleic acid.

Test accuracy

The November 2012 Minutes for Application 1161 considered that an assumption for modelling purposes of 100% sensitivity and 100% specificity for the test forming the evidentiary standard used in the key gefitinib trial (IPASS) overestimated the likely test performance across test options and pathology laboratories in Australia. This is relevant to the LUX Lung 3 afatinib trial as the same testing methodology was used. MSAC recommended that the sensitivity analyses of the economic evaluations presented to PBAC should appropriately examine the likely extent of proportions of false positive and false negative test results in Australia compared with those of the evidentiary standard because these proportions will have clinical and cost-effectiveness consequences due to the resulting misallocation of treatment.

The Final DAP noted that, as there is currently no reference standard for EGFR mutation testing, the evidentiary standard would be used to determine false positive and negative values for the current and proposed decision analysis.

However, the submission to PBAC did not address false positives and false negatives quantitatively in its economic evaluation. Instead it indicated that anecdotal evidence provided by expert pathologists at the October 2012 Stakeholder Meeting suggests that the incidence of false positive EGFR tests in Australian laboratories at present is very low/negligible, and that the accreditation requirements in place in Australia to support high quality testing substantially reduces the likelihood of false positive and negative results. Additionally, the proposed MBS restriction suggests "the use of a more sensitive method than Sanger sequencing" in samples with low tumour cell content to help further minimise false negative tests. Thus, the submission concluded that the clinical and economic consequences of false positive and false negative tests were expected to be small or negligible.

The sponsor further stated that the impact of test accuracy is more likely to relate to sensitivity rather than specificity. The inclusion of poor samples with too few tumour cells may lead to a false negative report, but is unlikely to result in a false positive report. False positives would most likely result from human error; e.g. cross contamination of samples or the reporting of mutations with unknown effects on EGFR TKI activity.

The potential for false negative or false positive reporting by Australian laboratories is very low based on the results of the RCPA Molecular Genetics Quality Assurance Program (QAP) Generic Report on EGFR, KRAS and BRAF mutation screening of human tumours, which became available on 5th September 2012 (RCPA 2008).

However, the QAP report does not provide any data on the accuracy of test results obtained in Australian diagnostic laboratories from poor quality samples containing less than 25% tumour tissue. The likelihood of a false negative result increases dramatically as the proportion of tumour material in a sample decreases below 20%. This can be overcome with the use of tumour enrichment techniques, such as Laser Capture Microdissection, which are utilised in some Australian laboratories.

11. Economic evaluation

The proposed MBS fee

November 2012 MSAC advice for Application 1161 suggested that, in the absence of any reason not to do so, the current MBS fee should apply to any expansion of eligibility for MBS funding of EGFR testing.

The submission did not request any changes to the current fee.

Cost-utility analysis

The submission to PBAC presented a modelled economic evaluation (cost-utility analysis in terms of incremental cost per QALY gained) based on the claim 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 November 2012 MSAC advice for Application 1161 recommended the following.

1. The economic evaluation presented to PBAC should reflect the fact that the effectiveness (of gefitinib) has only been demonstrated in randomised trial evidence for up to 70% of the prevalent EGFR activating mutations (that is, for exon 19 deletions and exon 21 L858R point mutations).
    - The base case economic evaluation presented in the submission to PBAC for afatinib was based on patients with "common" mutations only (exon 19 deletions and exon 21 L858R point mutations):
        - in the base case (without pemetrexed maintenance), with a 16% EGFR mutation prevalence, the incremental cost was in the range $45,000 - $75,000/QALY (additional cost of $**(redacted information)** per patient for **(redacted information)** QALYs gained per patient)
    - an alternative scenario was presented in the submission to PBAC that included patients with all EGFR mutations:
        - the incremental cost increased slightly within the range $45,000 - $75,000/QALY.

2. The base case of the economic evaluation and financial analysis presented to PBAC and MSAC should use 15% for the prevalence of activating EGFR mutations and the corresponding sensitivity analyses should examine a range of 10% to 20%.
   - The submission to PBAC conducted a cost-effectiveness analysis and used a prevalence of 16% for the base-case economic evaluation within the model.
   - The probabilistic sensitivity analysis examined a prevalence range of 12-20%, however, one-way sensitivity analyses for prevalence were not presented in the submission.
     - Sensitivity analyses with EGFR mutation prevalence of 12% and 20% were performed during evaluation:
       - with a 12% prevalence, the incremental cost decreased within the range $45,000 - $75,000/QALY
       - with a 20% prevalence the incremental cost increased within the range $45,000 - $75,000/QALY.

       MSAC considered that these results were counter-intuitive because the incremental cost-effectiveness ratio unexpectedly decreases as the prevalence decreases and increases as the prevalence increases.

3. The economic evaluation and financial analysis presented to PBAC and MSAC should include:
   i. a 12% re-biopsy rate
   ii. a 14% complication rate per biopsy
   iii. the costs of patient retrieval for re-biopsy, such as professional attendance fees, medical imaging or use of bronchoscopy.
   - In the submission to PBAC, the base case analysis in the economic evaluation and the financial analysis assumed that 8.7% of patients have insufficient tissue for testing, which was the observed re-biopsy rate with the DxS TheraScreen® EGFR 29 Mutation Detection Kit in the LUX Lung 3 trial. To account for other testing methodologies, sensitivity analyses in the economic evaluation were presented for arbitrarily chosen re-biopsy rates of 15 and 30%:
     - the re-biopsy rate associated with the use of real time PCR/direct DNA sequencing methodologies was estimated to be 15%, which increased the ICER within the range $45,000 - $75,000/QALY
       - the re-biopsy rate associated with the use of conventional Sanger DNA sequencing methodologies was estimated to be 30%, which increased the ICER to within the range $75,000 – $105,000/QALY
     - as DxS TheraScreen® EGFR 29 Mutation Detection Kit is only used in some diagnostic laboratories, the base case may not represent common practice in Australia.
   - The economic evaluation includes the costs for MBS items relating to obtaining the re-biopsy sample including cost of medical imaging/ bronchoscopy and costs for histology and EGFR mutation testing on the re-biopsy sample:
     - the cost of re-biopsy by ultrasound of $563.30, based on MBS Item 30710, was used for 100% of patients
     - the costs of retesting the histopathology and EGFR mutation status were $107.75 and $400, respectively
     - the total cost per re-biopsy was $1,017.07.

     As a bronchoscopy may require a hospital admission, AR-DRG codes for bronchoscopies were identified during the evaluation (E42A, E42B and E42C). The re-biopsy cost associated with the bronchoscopy same day AR-DRG (E42C, $1,793, see table below) should also have been considered in the submission to PBAC. Consequently, the total cost of re-biopsy may be underestimated.

Public hospital bronchoscopy data

DRG description	DRG	Separations	Total average cost
Bronchoscopy + CCC	AR-DRG Item E42A	887	$23,371
Bronchoscopy – CCC	AR-DRG Item E42B	2,615	$10,657
Bronchoscopy same day	AR-DRG Item E42C	6,343	$1,793

AR-DRG = Australian Refined Diagnosis Related Groups; CCC=catastrophic complication and/or co-morbidity.
Source: Public Sector Estimated Cost Weights Round 14 AR-DRG v6.0x (2009-10), National Hospital Cost Data Collection

- The submission used a literature based estimate for the complication rate during re-biopsy and estimated the complication rate from pneumothorax during re-biopsy as 9% and haemorrhage during re-biopsy as 1%. This would total to a complication rate of 10% rather than the 14% included in the MSAC advice.
  - The submission considered that 10% is not substantially different from 14%.
  - During the evaluation, the complication rate was increased to 14% (pneumothorax 12.6% and haemorrhage 1.4%) as per the MSAC advice, and the incremental cost slightly increased to within the range $45,000 - $75,000/QALY.
- The costs and disutilities associated with management of these adverse events for affected patients were included in the economic evaluation and the submission to PBAC claims that its estimates for complications are not substantially different but more detailed than the MSAC advice, in that specific complications are costed:
  - the estimated cost of managing pneumothorax during re-biopsy was $4,809.00
  - the estimated cost of managing a haemorrhage during re-biopsy was $2,907.53
  - the costs of treating the adverse events related to re-biopsy may be underestimated; bronchoscopies that require a hospital stay (see table above, AR-DRG E42A, $23,371 and E42B, $10,657) are substantially higher than the cost of bronchoscopies where the patient is discharged on the same day. The difference in cost may be due to the treatment of bronchoscopy-related adverse events. These were not considered in the submission.

4. The economic evaluations and financial analyses presented to PBAC and MSAC need not include any other repeat testing.
   - The submission agreed and an estimated average of one EGFR test per patient has been used in the economic evaluation and the financial analysis in the submission.

5. The economic evaluations and financial analyses presented to PBAC and MSAC should include the full costs of testing, such as patient episode initiation fees and any extra specimen enrichment.
   - The submission assumed that the MBS item includes the cost of macro and microdissection sample enrichment of the sample.
   - The submission's economic evaluation estimated the cost for EGFR mutation testing at $400 per test, with the weighted average fee applied (when determining the additional costs to the MBS for patient episode initiation fees and specimen referral fees) estimated at $16.27.

12. Financial/budgetary impacts

The listing of afatinib for first-line therapy would have little impact on the MBS as most patients with non-squamous NSCLC would be diagnosed with, or progress to, advanced disease and thus be eligible for MBS-funded EGFR mutation testing to determine their EGFR mutation status for second-line treatment with gefitinib. The costs to the MBS of the

proposed MBS and PBS listings associated with afatinib reflect the corresponding results of the submission to PBAC.

In order to estimate the number of patients that will require an EGFR mutation test, the incidence of lung cancer and the histological subtype was taken from the Australian Cancer Incidence and Mortality statistics (AIHW, 2011).

It was assumed that 62.8% of all lung cancers were NSCLC, and that of these 74.2% were adenocarcinoma or large cell carcinoma. In addition, 25.4% of all lung cancers were classed as 'other specified' or 'not otherwise specified' and may also be eligible for EGFR mutation testing.

The number of patients eligible for EGFR testing was estimated to less than 10,000 in the fifth year, with one test per patient assumed.

As EGFR testing for first-line access to afatinib is likely to substitute for EGFR testing for second-line gefitinib, the submission presented cost data for the anticipated incremental number of tests/re-biopsies performed and reduction in chemotherapy administration costs as a result of the introduction of afatinib.

The total cost to the MBS was estimated to be less than $2 million in the fifth year. With anticipated reductions in the use of platinum-based doublet chemotherapy, the net cost to the MBS was estimated to be less than $500,000 in the fifth year.

The submission's estimates are uncertain because:

- the second-line testing offset (60%) is likely to be an overestimate as the source of the current EGFR testing rate may include testing for access to first-line treatment (leakage)
- the proportion of patients undergoing re-biopsy may be an underestimate as it is based on rates of re-biopsy observed in LUX Lung 3
- the cost of re-biopsy may be an underestimate, as it does not consider bronchoscopies performed on hospital in-patients (see Section 11) or other costs associated with re-biopsy including professional attendance fees and the costs of retesting and of adverse events relating to re-biopsy
- the cost of testing may be underestimated as it does not include patient episode initiation or specimen referral fees
- the administration offset may be an overestimate due to the assumption of five cycles of chemotherapy administration, whereas clinical practice suggests the use of four
- the submission has not considered patient contributions for EGFR testing or chemotherapy administration nor has considered the safety net impact on the net financial implications to the MBS.

13. Key issues for MSAC

The financial implications to the MBS presented in the submission are likely to be underestimated.

14. Other significant factors

Nil.

15. Summary of consideration and rationale for MSAC's advice

MSAC noted that the July 2013 PBAC meeting had deferred its decision in relation to the listing of afatinib on the PBS, but had reaffirmed its intention to restrict such a listing to 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). MSAC reaffirmed the importance of aligning the population of patients eligible for testing with this restriction, although also allowing for EGFR mutation testing in non-squamous or NOS NSCLC at initial diagnosis rather than necessarily requiring that a patient waits until progression to locally advanced or metastatic disease before testing.

MSAC foreshadowed it would advise that the medication names "afatinib or gefitinib or erlotinib", or any appropriate sub-set thereof, would be used in the revised wording of an MBS item for EGFR mutation testing in the event of a PBAC recommendation to list any one or more of these medicines. MSAC did not prefer the alternative of "EGFR tyrosine kinase inhibitor" because it wanted to be able to review each new co-dependent linkage at this early stage of considering co-dependent test and medicine technologies. For example, it would want to consider the "evidentiary standard" test for each subsequent new treatment option (the test used to identify the EGFR mutation status in the key trials supporting the new treatment option) and to consider the means through which the treatment option achieves its effect.

MSAC rejected any proposal to include "tumour cells" rather than "tumour tissue" to define the source of the specimen for EGFR mutation testing. In particular, MSAC advised that EGFR mutation testing should not be subsidised when the source of the specimen is circulating tumour cells. Suitable specimens include a tissue biopsy of the lung cancer which would include cytology blocks.

MSAC reaffirmed its November 2012 advice that the proposed MBS item should be made a pathology determinable service so that the pathologist can perform EGFR mutation testing on samples which meet the requisite histological criteria. This process ensures that the diagnostic process is not interrupted by the need to get a referral from a clinician for mutation testing. This supports MSAC's preference that EGFR mutation testing be performed on the same specimen in the same laboratory as the prerequisite histology testing because this would optimise both confidence in pathology results and parsimonious use of the specimen. It is also consistent with MSAC's previous advice that pathology practice should be optimised through a more centralised approach to ensure EGFR mutation testing is limited to laboratories with appropriate expertise and back-up. However, MSAC did not change its advice on the text for the proposed MBS item descriptor to require that the one laboratory performs both the histology and genetic testing on the specimen. Similarly, although MSAC reaffirmed its November 2012 advice that biopsy sampling practice should also be optimised to obtain sufficient tumour tissue of adequate quality to obtain high rates of satisfactory specimens.

MSAC noted that the economic evaluations and financial analyses presented to the July 2013 PBAC meeting generally followed its November 2012 advice including on the prevalence of activating EGFR mutations (15%), re-biopsy rate (12%), costs for re-biopsy, complication rate for re-biopsy (14%), costs for testing, and the need for sensitivity analyses of the likely extent of proportions of false positive test results and false negative test results in Australia. However, the corresponding submission to PBAC for afatinib used a prevalence of activating EGFR mutations of 16%, a re-biopsy rate 8.75%, and a complication rate for re-biopsy of 10%, which explained some of the differences between the resulting economic evaluations and financial analyses. The corresponding submission to PBAC for afatinib also did not appropriately examine the likely extent of proportions of false positive test results and false negative test results in Australia in sensitivity analyses.

MSAC reaffirmed its November 2012 advice that, in the absence of any reason not to do so, the current MBS fee should apply to any expansion of eligibility for MBS funding of EGFR mutation testing. MSAC noted the applicant's estimates of financial implications to the MBS of $0.8 million to $0.4 million per year, and considered that they were underestimates.

MSAC recalled its November 2012 advice to collect data on the prevalence of various types of detected EGFR mutations and to support the clinical basis for determining whether they predict sensitivity or resistance to subsequent TKI therapy. MSAC noted that representatives of the National Health and Medical Research Council, MSAC, PBAC and the Department had met to discuss targeted data collection relating to BRAF mutation testing and BRAF inhibitor treatment as proposed by PBAC in March 2013 and supported by MSAC in April 2013.

MSAC reaffirmed its advice that such data collection be also applied to EGFR mutation testing and EGFR TKI treatment, noting that the proportion of EGFR mutations which had not been included in the evidentiary EGFR TKI trials was likely to be significant (e.g if benchmarked against BRAF mutations, the proportion predicted is likely to be greater than the proportion of BRAF V600 mutations which had not been included in the BRAF inhibitor trials).

MSAC noted that the key randomised trial providing the evidence of effectiveness for afatinib (the LUX Lung 3 Study) relied on the DxS TheraScreen® EGFR 29 Mutation Detection Kit (which uses Scorpion-ARMS technology) to determine the EGFR status screened tumours from subjects with NSCLC, with mutation positive individuals recruited as trial participants. This test was also used in the IPASS study of gefitinib and is also one of the options used in Australian pathology laboratories.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of epidermal growth factor receptor (EGFR) mutation testing to help determine eligibility for proposed PBS-subsidised afatinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC again deferred the application for the requested MBS item until such time as PBAC makes a decision regarding the corresponding PBS listing of afatinib. MSAC advised that, if PBAC subsequently decides to recommend to the Minister that afatinib be listed on the PBS for the treatment of advanced NSCLC, it would support an expedited process for reconsideration to align MSAC support for public funding of EGFR testing according to the circumstances recommended by PBAC. MSAC foreshadowed its support for public funding to be achieved by modifying MBS item 73328. The MBS fee of $397.35 would be retained, but the item descriptor would be amended to include:

A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to afatinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC reiterated that it would support an expedited MSAC process of re-consideration if PBAC subsequently recommends PBS listing. MSAC also reaffirmed its November 2012 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent

health technologies, appropriate data be collected prospectively to be reviewed two years after listing.

Out-of-session MSAC consideration – November 2013

Application No. 1293 - Epidermal Growth Factor Receptor (EGFR) testing to determine eligibility for afatinib treatment in patients with locally advanced or metastatic non-small-cell lung cancer

Summary of consideration and rationale for MSAC's advice

MSAC deferred this application at its 1 August 2013 meeting. MSAC's consideration was coordinated with PBAC consideration of afatinib on 9-12 July 2013. On 1 August 2013, MSAC indicated support for the proposal to modify the existing MBS item for EGFR mutation testing, but deferred provision of formal advice to the Minister until such time as MSAC advice could be coordinated with a PBAC recommendation to list afatinib on the PBS.

The MSAC Chair and Secretariat were advised that PBAC recommended PBS listing for afatinib as first-line treatment of locally advanced or metastatic NSCLC in patients with EGFR gene mutation(s).

MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of epidermal growth factor receptor (EGFR) mutation testing to help determine eligibility for proposed PBS-subsidised afatinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC advised that the item descriptor for MBS item 73328 be amended to read as below:

A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to erlotinib or gefitinib ***or afatinib*** *under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

MSAC reaffirmed its November 2012 and August 2013 advice that the proposed MBS item should be made a pathologist determinable service.

MSAC advised that the MBS fee of $397.35 should be retained.

MSAC reaffirmed its August 2013 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively.

17. Applicant's comments on MSAC's Public Summary Document

No comment.

18. Context for decision

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.