



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1173 – Testing for epidermal growth factor receptor (EGFR) status in patients with locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC) for access to erlotinib

Sponsor/Applicant/s: Roche Products Pty Ltd

Date of MSAC consideration: 1 August 2013

1. Purpose of application

In March 2013, the Department of Health and Ageing received an application from Roche Products Pty Limited requesting Medicare Benefits Schedule (MBS) listing of epidermal growth factor receptor (EGFR) mutation testing for non-squamous non-small-cell lung cancer (NSCLC) to determine eligibility for first-line treatment with erlotinib, 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 was 70%: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 erlotinib, 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. The applicant requested MBS listing of EGFR mutation testing for non-squamous NSCLC to determine eligibility for first-line treatment with erlotinib, through 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

In 2008, PBAC recommended the use of erlotinib as a monotherapy in unselected patients with non-small cell lung cancer (NSCLC) who had failed prior chemotherapy.

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.

Erlotinib was proposed for the first-line treatment of patients with advanced (stage IIIb) or metastatic (stage IV) NSCLC with activating epidermal growth factor receptor (EGFR) mutations in 2012. A co-dependent submission for public funding of erlotinib and the EGFR mutation test was considered by PBAC in July 2012 and MSAC in August 2012 under the then pilot co-dependent technology assessment process.

At the August 2012 meeting, MSAC did not support the listing of EGFR mutation testing for determining eligibility for erlotinib treatment as a first-line therapy in patients with locally advanced or metastatic NSCLC. MSAC ‘advised the Minister that it does not support public funding for this indication on the basis of insufficient evidence to determine the comparative performance and costs across the testing options and their consequences for the comparative effectiveness and cost-effectiveness of erlotinib’.

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.

Following the November 2012 MSAC meeting, which discussed Application 1161 (EGFR mutation testing for first-line treatment with gefitinib), and taking the advice received from the stakeholder meeting, the MSAC outcome was more supportive of EGFR testing than reflected in the previous (August 2012) MSAC minutes for Application 1173 in relation to EGFR testing for access to erlotinib, as many concerns raised previously were resolved during the stakeholder meeting.

Given this development, the applicant was advised that only a “minor” resubmission to MSAC was required to address outstanding testing issues raised in the November 2012 MSAC minutes, pertinent for the MBS listing of EGFR testing for access to erlotinib as first-line therapy in locally advanced or metastatic NSCLC.

3. Prerequisites to implementation of any funding advice

No specific test was requested in the resubmission for MBS listing. 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 resubmission requested a change to the current MBS listing as detailed below. The resubmission stated that the proposed MBS item descriptor for EGFR mutation testing is consistent with the MSAC advice to the Minister, in tumour tissue from a patient with NSCLC which is non-squamous or not otherwise specified is tested for activating EGFR mutations at initial diagnosis. The resubmission also stated that “the MBS item descriptor should exclude reference to the current PBS subsidised access to erlotinib as a second-or third-line treatment, which does not have a requirement for determination of EGFR mutation status”.

Table 1 Current and proposed MBS item descriptor for EGFR mutation testing

Current MBS item descriptor for second-line 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 erlotinib

73328

A test of tumour tissue from a patient with non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise specified, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for first-line access to erlotinib are fulfilled once the patient is also diagnosed with locally advanced or metastatic disease.

Fee: \$[400]

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 1 of minor resubmission to MSAC

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 restrictions for erlotinib for consideration at the July 2013 PBAC meeting are as follows:

Section 85 authority required

Initial PBS-subsidised treatment, as monotherapy, for the first-line treatment of locally advanced (stage IIIb) or metastatic (stage IV) non-squamous or not otherwise

specified (NOS) non-small cell lung cancer in patients where there is evidence that the patient has an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material.

Section 85 authority required

Continuing PBS-subsidised treatment, as monotherapy, of a patient who has previously been issued with an authority prescription for erlotinib and who does 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 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 resubmission agreed with MSAC.

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 resubmission commented that a Quality Assurance Program run by the Royal College of Pathologists of Australasia is in place for EGFR mutation testing in Australia and that the National Association of Testing Authorities also has a certification program for molecular tests.

5. Consumer Impact Statement

PASC received one response during the public consultation period for the DAP from a medical specialist. The concerns raised included: the classification and eligibility for treatment of secondary 'TKI resistant' EGFR mutations and the true cost of EGFR mutation testing being in excess of \$400 per test.

6. Proposed intervention's place in clinical management

EGFR mutation testing would be used to identify a subgroup of patients with locally advanced or metastatic non-squamous or NOS NSCLC who would likely benefit from first-line treatment with erlotinib.

EGFR mutation testing for access to first-line TKIs will result in some additional testing because at the time of the application testing only occurred 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 erlotinib, while those who do not have an EGFR mutation would receive platinum doublet chemotherapy.

Prevalence of EGFR mutations in NSCLC

November 2012 MSAC advice for Application 1161 recommended that an EGFR mutation prevalence of 15%, with a range of 10% to 20% for sensitivity analysis, should be presented to PBAC. The resubmission agreed with this and used these values in the economic evaluation and financial analyses presented in the resubmission to PBAC.

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 resubmission agreed with MSAC; the proposed MBS item descriptor and the clinical management algorithm presented in the resubmission to PBAC reflect this.

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 resubmission did not comment on this.

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.

- Based on the above advice, a 70% rate for common mutations and a 30% rate for rare mutations was used in the base-case economic evaluation and financial analyses presented in the resubmission to PBAC.
- The resubmission to PBAC stated that a proportion of 70% of common mutations is not aligned with the proportion found in current Australian clinical practice and from the published literature. The resubmission proposed that no more than 20% of patients have rare mutations, and that this estimate would be more appropriate for inclusion in the cost effectiveness analysis.
- The resubmission to PBAC suggested that the use of EGFR mutation-specific tests, such as the Cobas® EGFR Mutation Test would limit the number and proportion of patients with rare EGFR mutations identified in clinical practice.

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 resubmission agreed with MSAC, and this was reflected in the proposed MBS item descriptor and the proposed clinical management algorithm presented in the resubmission to PBAC.

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.

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 resubmission.

The November 2012 MSAC advice for Application 1161 agreed that the nominated comparator of no EGFR testing was appropriate.

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, patients diagnosed with non-squamous or not otherwise specified NSCLC would undergo EGFR mutation testing to determine eligibility for erlotinib as a first-line therapy for those who are EGFR mutation positive on diagnosis of, or progression to, stage IIIb or stage IV disease.

The resubmission proposed that, in the scenario where gefitinib is not PBS listed for the first-line treatment of locally advanced or metastatic NSCLC in patients with activating EGFR mutations, platinum-based doublet chemotherapy is the appropriate comparator for erlotinib.

However, in the scenario where gefitinib is PBS listed for the first-line treatment of locally advanced or metastatic NSCLC in patients with activating EGFR mutations, gefitinib is the appropriate comparator for erlotinib. Furthermore, the resubmission acknowledged that, in addition to gefitinib, afatinib should also be considered as a comparator but was not

included due to time constraints between publication of the Final DAP for afatinib on 5 March 2013, and the March 2013 lodgement deadline for resubmissions.

9. Comparative safety

The main safety concern with EGFR testing is the need to re-biopsy as this can result in complications such as pneumothorax and haemorrhage, which were considered to occur in 14% of re-biopsy cases.

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. The economic evaluation presented to PBAC assumed a 12% invalid test rate in the base-case and assumed all invalid tests lead to a re-biopsy. Sensitivity analysis used an 8.1% re-biopsy rate to reflect the invalid test rate at the Peter McCallum Institute, which uses Sanger DNA sequencing. Also assumed was that only 80% of patients would be eligible to be re-biopsied, and that there is a 14% re-biopsy complication rate. This is in line with MSAC recommendations. 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. The evidentiary standard used in the key EURTAC trial were 3 laboratory-developed tests: PCR fragment length analysis of exon 19 deletions, a TaqMan-based PCR assay for exon 21 L858R point mutation, and secondary Sanger DNA sequencing.

A summary of the EGFR mutation testing methods used in the main EGFR clinical trials and in Australian laboratories are shown in the table below.

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

Clinical trial/ Pathology laboratory	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)
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)
First-SIGNAL	DNA sequencing of exons 19, 20 and 21 (repeated to confirm)
NEJ002	PNA-LNA PCR clamp
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 MSAC advice 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. 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.

A study, presented at the American Society of Clinical Oncology Conference in 2012 (Benlloch et al. 2012), evaluated the diagnostic accuracy of the EURTAC patient screening method by retesting tumour samples from patients in the EURTAC screening population with three other tests: the Cobas® EGFR Mutation Test, Sanger DNA sequencing, and massively parallel pyrosequencing (a next generation sequencing method). The comparison of the EURTAC laboratory-developed tests with the tests used in Australian diagnostic laboratories (Cobas® EGFR Mutation Test and Sanger DNA sequencing) was used in the resubmission to PBAC to estimate the false positive and false negative rates for use in the economic model.

- The base case model in the resubmission to PBAC assumed that the Cobas® EGFR Mutation Test is used to determine which patients receive erlotinib as first-line therapy.
 - The diagnostic accuracy was calculated using the results of the Cobas® EGFR Mutation Test compared to the EURTAC laboratory-developed tests, as reported by Benlloch et al. 2012.
 - However, the resubmission extrapolated the data to take account of the difference between the EGFR mutation positive prevalence of eligible patients in the EURTAC screening population compared to the sampling proportion for the Cobas® EGFR Mutation Test.
 - Thus, the diagnostic accuracy data used for the base case in the economic evaluation (based on an EGFR mutation prevalence of 22.1%) was recalculated.
 - MSAC considered that the reason for this extrapolation in determining diagnostic accuracy is unclear and of uncertain validity, as the positive and negative predictive values should be determined using the prevalence rate of the Australian population.
 - When calculated using the Cobas® EGFR Mutation Test sensitivity and specificity and the MSAC recommended EGFR mutation prevalence of 15% for the Australian population, different positive and negative predictive values were obtained.
- The diagnostic accuracy using the results of the Cobas® EGFR Mutation Test compared to the EURTAC laboratory-developed tests as reported by Benlloch et al. 2012 were extrapolated for the whole EURTAC screening population and incorporated into sensitivity analyses conducted in the resubmission to PBAC.
- The diagnostic accuracy of Sanger sequencing versus the EURTAC laboratory-developed tests using the EURTAC screening population was calculated in the resubmission and incorporated into sensitivity analyses.

- When calculated using above sensitivity and specificity and the MSAC recommended EGFR mutation prevalence of 15% for the Australian population, different positive and negative predictive values were obtained.
- The diagnostic accuracy of the Cobas® EGFR Mutation Test versus massively parallel pyrosequencing using a subset of samples from the EURTAC trial was also calculated in the resubmission screening population and incorporated into sensitivity analyses.
 - However, this subset of samples from the EURTAC trial had a 37% EGFR mutation prevalence.
 - Thus, when calculated using the above sensitivity and specificity and the MSAC recommended EGFR mutation prevalence of 15% for the Australian population, different positive and negative predictive values were obtained.

MSAC considered that the use of the Benlloch et al (2012) study to determine diagnostic accuracy was flawed due to the imperfect evidentiary standard against which the test accuracy was estimated. EGFR mutation testing for the EURTAC trial was designed to detect only the common exon 19 deletion and exon 21 L858R mutations.

In the Australian clinical setting, 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, this 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 resubmission for erlotinib suggested that the cost of EGFR mutation testing (using the Cobas® EGFR Mutation Test) in Australia is estimated to be \$400 per patient.

Cost-effectiveness analysis

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 resubmission for erlotinib claimed that a 70%:30% ratio for common versus rare EGFR mutations would represent a future scenario that would grow the denominator or prevalence pool of all patients with EGFR activating mutations. This would be due to the increase in the number of patients with newly identified rare mutations over and above those who would presently be identified as eligible patients. As a consequence, the resubmission increased the prevalence of activating EGFR mutations in patients with non-squamous or not otherwise specified NSCLC from 15% in Year 1 to 17.6% in Years 2 to 5.
 - The resubmission to PBAC presented a cost effectiveness analysis for the common mutations, using EURTAC phase III clinical trial data:
 - for ‘base case 1’, without pemetrexed maintenance, the incremental cost was in the range \$45,000 – \$75,000/QALY (cost of \$(**redacted information**) per patient for (**redacted information**) QALYs gained per patient)
 - for ‘base case 2’, where pemetrexed maintenance is included in (**redacted information**)% of cases, erlotinib was estimated to be dominant (estimated cost saving of \$(**redacted information**) per patient for (**redacted information**) QALYs gained).
2. The base case economic evaluation and financial analyses presented to PBAC should use 15% for the Australian prevalence of activating EGFR mutations and the corresponding sensitivity analyses should examine a range of 10% to 20%.
- This has been addressed in the resubmission to PBAC by presenting a cost-effectiveness analysis using a prevalence of 15% for the base-case modelled economic evaluation, using the COBAS test. It is unlikely that any imperfect test would have the ability to identify EGFR mutation positive patients with an accuracy that reflects the true prevalence. Furthermore, the positive predictive value (named as true positive rate in the model) used in the model was calculated using the prevalence of EGFR positive mutations in the trial, which is 22%.
 - The economic model is highly sensitive to changes in the prevalence rate:
 - with a 10% prevalence, the incremental cost in ‘base case 1’ increases from within the range \$45,000 – \$75,000/QALY to be within the range \$105,000 – \$200,000/QALY and ‘base case 2’ changes from being dominant to an incremental cost in the range \$15,000 - \$45,000/QALY
 - with a 20% prevalence, the incremental cost in ‘base case 1’ decreases to within the range \$45,000 – \$75,000/QALY and ‘base case 2’ remains dominant for erlotinib.
- MSAC considered that some of these results were counter-intuitive (where the incremental cost-effectiveness ratio unexpectedly becomes more favourable as the prevalence decreases and becomes less favourable as the prevalence increases).
3. The economic evaluations and financial analyses presented to PBAC 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.
- The base case economic model in the resubmission to PBAC assumed a 12% invalid test rate and assumed all invalid tests lead to a re-biopsy with a 14% complication rate and all are retested.
 - The resubmission reported that a 12% re-biopsy rate may overestimate current clinical practice in Australia. The re-biopsy rate is expected to drop even further with improved testing methods in the future.

- A sensitivity analysis of the model used an 8.1% re-biopsy rate to reflect the invalid test rate at the Peter McCallum Institute, which uses Sanger DNA sequencing. The model assumed that only 80% of patients would be eligible to be re-biopsied, with a 14% complication rate. The remaining 20% were assumed to require block retrieval and retesting:
 - the 'base case 1' incremental cost decreased from within the range \$45,000 – \$75,000/QALY to be within the range \$15,000 – \$45,000/QALY
 - 'base case 2' remained dominant for erlotinib.
4. The economic evaluations and financial analyses presented to PBAC and MSAC need not include any other repeat testing.
 5. The economic evaluation and financial analyses presented to PBAC and MSAC should include the full costs of testing, such as patient episode initiation (PEI) fees and any extra specimen enrichment.
 - The resubmission agreed and the economic evaluation includes the full costs associated with testing including a specimen referral fee and PEI fees.
 - For the purposes of the resubmission, the average current chemotherapy treatment rate for patients with NSCLC in the private hospital setting ((**redacted information**)%) is used as a proxy for the proportion of biopsies undertaken privately. Thus (**redacted information**)% of patients attract a \$2.40 PEI fee.
 - The remaining (**redacted information**)% are assumed to have a PEI fee applied as an outpatient of a public hospital, attracting an \$8.20 fee.
 - The resubmission assumed that macro and microdissection sample enrichment is included as part of the MBS item cost.
 - There is currently no item number for block retrieval. The resubmission included the cost of block retrieval as part of the cost estimate for re-biopsy within the economic model and financial estimates. It was estimated to be \$(**redacted information**), through consultation with pathologists.
 - The resubmission's economic evaluation did not use the revised cost of EGFR mutation testing, which was reduced to \$397.35 on 1 January 2013. The previous cost was \$400 per patient plus a PEI fee of \$3.56 and a specimen referral fee of \$10.30. Thus, an EGFR mutation test was estimated to cost a total of \$413.86. This small difference did not have a significant impact on the results of the economic evaluation.

12. Financial/budgetary impacts

The listing of erlotinib for first-line therapy would have an impact on the MBS as patients with non-squamous or not otherwise specified NSCLC would undergo MBS-funded EGFR testing to determine their EGFR mutation status at the time of diagnosis. The costs to the MBS of the proposed MBS and PBS listings associated with erlotinib reflect the corresponding results of the resubmission to PBAC.

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

The number of patients eligible for EGFR testing was estimated by the resubmission to be less than 8,000 in the fifth year. The estimated costs of EGFR mutation testing to the MBS include incidental fees and retesting (after re-biopsy). The resubmission did not consider cost offsets to the MBS due to the proposed listing of erlotinib.

The total cost to the MBS was estimated to be less than \$3 million in the fifth year.

All the costs associated with re-biopsy were assumed to be incurred by state and territory health budgets. The cost for re-biopsy was estimated to be less than \$5 million in the fifth year.

13. Key issues for MSAC

The economic model presented in the resubmission to PBAC is sensitive to changes in the prevalence of EGFR mutations. A decrease in the prevalence from 15% to 10% increases the ICER from within the range \$45,000 – \$75,000 per QALY to within the range \$105,000 – \$200,000 per QALY.

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 modifying the listing of erlotinib 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 “erlotinib or gefitinib or afatinib”, 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, 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.

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 \$2.8 million to \$3.0 million per year.

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).

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 first-line erlotinib 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 erlotinib. MSAC reiterated that, if PBAC subsequently decides to recommend to the Minister that erlotinib be listed on the PBS for the first-line 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 erlotinib 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 – September 2013

Application 1173 - Testing for epidermal growth factor receptor (EGFR) status in patients with locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC) for access to erlotinib

Summary of consideration and rationale for MSAC's advice

MSAC deferred this application at its meetings on 2 August 2012 and 1 August 2013. MSAC's considerations were coordinated with PBAC considerations of erlotinib on 11-13 July 2012 and 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 modify the existing PBS items for erlotinib.

The MSAC Chair and Secretariat were advised that, on 20 September 2013, PBAC recommended that the PBS listing for erlotinib be modified to include subsidy for its use for EGFR mutation positive advanced NSCLC.

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 determine eligibility for proposed PBS-subsidised first-line erlotinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC advised that the item descriptor for MBS item 73328 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 erlotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC reaffirmed its 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

Roche welcomes the MSAC decision to support MBS listing of EGFR mutation testing at diagnosis, irrespective of disease stage, to determine eligibility for PBS-subsidised erlotinib in patients with locally advanced or metastatic non-squamous or NOS EGFR-positive NSCLC. Roche also acknowledges that a pragmatic decision has been taken which allows pathologists to request the EGFR test without being interrupted to get a referral from a clinician.

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.