National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Afatinib for the treatment of epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Boehringer Ingelheim	Yes, this is an appropriate topic for appraisal. This topic addresses an area of NHS priority (the treatment of lung cancer) and there is a clear unmet need particularly for those patients whose cancer has progressed after their second line of treatment.	Comment noted.
	Royal College of Pathologists	It is appropriate.	Comment noted.
	The Royal College of Nursing	Yes I feel that it would be appropriate to refer to NICE	Comment noted.
Wording	Boehringer Ingelheim	Yes, the wording is appropriate.	Comment noted.
	AstraZeneca UK Ltd	The remit needs to be clearer whether the objective is to appraise afatinib in both first and second line or to have two separate appraisals one for first line and one for second line.	NICE can only issue guidance in line with marketing authorisation. At present the exact marketing authorisation is unknown therefore there is a need for the remit to be broad. No changes were made to this section.
	Royal College of Pathologists	Yes	Comment noted.

Appendix D - NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
Timing Issues	Boehringer Ingelheim	None anticipated; the timing is appropriate.	Comment noted.
	AstraZeneca UK Ltd	Would recommend a MTA looking at both first and second line positioning which may have implications on the timings of the availability of the guidance.	We do not know at this stage the proposed marketing authorisation for afatinib. The remit at present covers a single indication 'EFGR positive NSCLC'. Workshop attendees discussed the other appraisals on-going at NICE for EFGR positive NSCLC and the implications on the timings of the availability of the guidance.
Additional comments on the draft remit	Boehringer Ingelheim	No additional comments	Comment noted.
	Eli Lilly and Company Limited	It is not very clear if appraisal is first-line/second-line or both. The section on comparators includes both first-line and second-line agents. The background information includes information on first-line, second-line and maintenance treatment. The scope needs to specify line/lines of treatment clearly to determine the most appropriate comparators.	The line of treatment was not specified by the Manufacturer. NICE will only issue guidance in line with the marketing authorisation for a drug. The line of treatment will be confirmed upon approval of the license by the regulatory body. Third and fourth line comparisons have also been included in the scope.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Boehringer Ingelheim	Yes, this section appears accurate.	Comment noted.
	Roche Products Limited	The draft scope states that the NICE Appraisal of erlotinib for the first line treatment of EGFR-TK mutation positive advanced or metastatic non-small-cell lung cancer is ongoing - this appraisal is now complete (NICE TA258). Erlotinib is now NICE recommended as an option for the first line treatment of this patient population. The scope should be updated to reflect the completion of this Appraisal.	The scope has been updated to reflect that the Erlotinib appraisal is now complete and guidance has been published.
	Royal College of Pathologists	Accurate and complete	Comment noted.
The technology/ intervention	Boehringer Ingelheim	No, the following should be added to the description of the technology: "Afatinib inhibits signalling from all homo- and heterodimers formed by the ErbB family members: EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4." In addition the information relating to the clinical trials is incorrect as it does not distinguish between traditional chemotherapy and targeted therapies, and does not include the current status of all studies. The draft scope states the following: "It is currently being studied in clinical trials compared with chemotherapy (gefitinib, cisplatin plus gemcitabine, cisplatin plus pemetrexed, erlotinib) in adults for the treatment of EGFR mutation positive locally advanced or metastatic non-small cell lung cancer." We suggest replacing this wording with the following: "Afatinib is currently being studied in comparison to chemotherapy regimens and to targeted therapies. Chemotherapy comparison studies: There is an ongoing study in Asia (Lux-Lung 6) comparing afatinib with	The scope has been updated to include the HER3 and HER4 members of the ErbB family. It has also been amended to differentiate between chemotherapy and targeted therapies. However the technology description in the scope does not aim to provide full details of the pharmacological action of the drug or the full details of the clinical trials.

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		cisplatin plus gemcitabine. The Lux-Lung 3 clinical trial comparing afatinib to cisplatin plus pemetrexed has reported its primary endpoint. Data collection and analysis is ongoing and will be published in the future. EGFR TKI comparison studies: Afatinib is being evaluated in patients with EGFR mutations compared to gefitinib in the Lux-Lung 7 clinical trial. Afatinib is also being compared with erlotinib in the second line setting in patients with advanced squamous cell carcinoma however this trial is not applicable for this technology appraisal."	
	Roche Products Limited	The draft scope states that afatinib 'is currently being studied in clinical trials compared with chemotherapy (gefitinib, cisplatin plus gemcitabine, cisplatin plus pemetrexed, erlotinib) in adults ….'. This statement is inaccurate - erlotinib and gefitinib are targeted agents and not chemotherapies. We suggest the scope be amended with the following wording: afatinib 'is currently being studied in clinical trials compared with chemotherapy (cisplatin plus gemcitabine, cisplatin plus pemetrexed) and targeted agents (erlotinib, gefitinib) in adults …'.	The scope has been amended to differentiate between the chemotherapy drugs and targeted therapies.
	Royal College of Pathologists	Yes	Comment noted.
Population	Boehringer Ingelheim	Yes, this is appropriately defined.	Comment noted.
	AstraZeneca UK Ltd	Please amend population to epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation positive in line with previous appraisals in this population.	The population has been amended to epidermal growth factor receptor tyrosine kinase mutation positive.
	Royal College of Pathologists	Definition is appropriate	Comment noted

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Comparators	Boehringer Ingelheim	No, these are not the standard treatments currently used in the NHS. First line treatment for EGFR mutation patients: Data from IMS Oncology Analyser MAT Q1 2012 shows that 97% of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with positive epidermal growth factor receptor (EGFR) mutation receive 1st line treatment with erlotinib or gefitinib. The chemotherapy regimens of gemcitabine, docetaxel, paclitaxel or vinorelbine in combination with carboplatin or cisplatin are therefore not appropriate comparators for this specific EGFR mutation positive population and should be removed from the scope. The above IMS data shows that for those remaining EGFR mutation positive patients not receiving treatment with EGFR TKIs (namely erlotinib or gefitinib), cisplatin plus pemetrexed is the chemotherapy that is used. This chemotherapy comparator is therefore still a valid comparator for this appraisal and should be explicitly stated as such. Second line treatment for EGFR mutation patients: The specified second line treatments stated in the draft scope are the standard treatments used in the NHS. It should be noted that these treatments are recommended by NICE for the whole population of advanced or metastatic NSCLC patients rather than specifically for EGFR mutation patients. Third line treatment for EGFR mutation patients: No comparator has been suggested for third line treatment. In the absence of any NICE recommended drug the only comparator to afatinib in this setting is best supportive care. A third line comparison versus best supportive care should therefore be included in the scope.	The comparators have been updated in line with the consultation comments and the discussions at the scoping workshop. The comparators were specified according to the line of treatment (first, second and third/ fourth line). This is because the potential indication for afatinib in terms of the line of treatment is yet to be confirmed.
	AstraZeneca UK Ltd	The comparators are valid	Comment noted.
	Eli Lilly and Company Limited	To ensure consistency in the appraisal of all EGFR TKIs, pemetrexed/cisplatin should not be considered a comparator to afatinib in the first-line treatment of EGFR positive non-squamous NSCLC patients in this appraisal.	The comparators have been updated in line with the consultation comments and

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		Pemetrexed/cisplatin is currently used in the NHS as first-line chemotherapy only in EGFR negative patients with non-squamous histology. Patients who are EGFR positive would not receive pemetrexed/cisplatin first-line in routine clinical practice, but would instead receive gefitinib or erlotinib. During the recent technology appraisal of erlotinib in first-line EGFR positive NSCLC (TA258), clinical specialists stated that pemetrexed/cisplatin was rarely used as first-line treatment in this patient population. The appraisal committee accepted this view as a result of which pemetrexed/cisplatin was deemed not to be an appropriate comparator to erlotinib.	the discussions at the scoping workshop. The comparators were specified according to the line of treatment (first, second and third/ fourth line). This is because the potential indication for Afatinib in terms of the line of treatment is yet to be confirmed.
	Roche Products Limited	Doublet chemotherapy is not a relevant comparator to EGFR tyrosine kinase inhibitors (i.e. erlotinib, gefitinib or afatinib) in the first treatment of EGFR-TK mutation positive advanced or metastatic non-small cell lung cancer. Market research indicates that over 95% of patients with EGFR-TK mutations receive erlotinib or gefitinib as a first line treatment. This issue was discussed by the Appraisal Committee in NICE TA258. In this Appraisal the Committee concluded that doublet chemotherapy was not an appropriate comparator for erlotinib - in light of this we suggest the doublet chemotherapies are removed from the scope for afatinib. In the second line setting very few EGFR-TK mutation positive patients will be naïve to an EGFR TKI (i.e. erlotinib and gefitinib) - it is standard clinical practice to use one of these agents as a first line treatment in this patient population and so less than 1 in 20 patients would be expected to be EGFR TKI naïve at second line. In light of this we would question the value of evaluating afatinib at all in the second line setting. Only if afatinib is granted a licence for re-treatment of patients who received an EGFR-TKI first line would a second line evaluation seem to be valuable.	The comparators have been updated in line with the consultation comments and the discussions at the scoping workshop. The comparators were specified according to the line of treatment (first, second and third/ fourth line). This is because the potential indication for Afatinib in terms of the line of treatment is yet to be confirmed.
	Royal College of Pathologists	Yes.	Comment noted.
Outcomes	Boehringer Ingelheim	Yes, these outcomes are appropriate.	Comment noted.
	AstraZeneca UK Ltd	Adverse effects of treatment should include costs of treatments alongside effect on health-related quality of life (HRQoL)	Comment noted.

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	Royal College of Pathologists	Yes	Comment noted.
Economic analysis	Boehringer Ingelheim	This is appropriate.	Comment noted.
	AstraZeneca UK Ltd	Cost of testing should also be included in the economic analysis in line with previous appraisals in this population	Comment noted.
Equality	Boehringer Ingelheim	None identified.	Comment noted.
	AstraZeneca UK Ltd	Nothing further to add	Comment noted.
	Royal College of Pathologists	No equality issues identified	Comment noted.
Other considerations	Boehringer Ingelheim	None identified.	Comment noted.
	Eli Lilly and Company Limited	Currently, the duration of treatment with EGFR TKIs is unclear from the data available. Since the cost of afatinib and the outcomes would depend on the duration of treatment, the actual duration of treatment in routine clinical practice should also be considered.	Comment noted.
Innovation	AstraZeneca UK Ltd	No innovation demonstrated – although first in class with an alternative mechanism of action, afatinib offers significant tolerability issues and marginal clinical benefit to patients	Comment noted.
	Roche Products Limited	No. Afatinib is not a 'step-change' in the treatment of mNSCLC. There are already two NICE approved EGFR tyrosine kinase inhibitors available for use in this patient population.	Comment noted.
	Royal College of Pathologists	The technology is innovative and could impact on quality of care. Benefits should be adequately covered by the QALY calculation.	Comment noted.

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	The Royal College of Nursing	I feel that Afatinib could be considered as an alternative to other first line treatments currently in use All comparators appear to be included It should be considered as it may potentially have fewer, more tolerable side-effects when compared to current treatment It may be able to be given in a setting closer to the patient's home would be more acceptable to patients and have a physical, psychological and economic benefit to patients	Comment noted.
Questions for consultation	Boehringer Ingelheim	The proposed indication for afatinib is for the treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation(s). It therefore follows that afatinib could be used in first, second, or third line treatment for this subgroup of patients. For comments on the appropriateness of the comparators please refer to the comment in the comparators sub-section above. The population defined for this appraisal is for people with locally advanced or metastatic NSCLC with positive EGFR mutation. This cohort represents a small subgroup of patients with lung cancer for whom afatinib is targeted. Therefore we do not envisage that undertaking further subgroup analyses would be necessary or informative.	Comment noted. NICE will only appraise this technology within its licensed indication. The attendees at the scoping workshop noted that the EGFR mutation positive cohort is a small group of patients; hence they did not consider any analysis based on subgroups to be particularly necessary.
	AstraZeneca UK Ltd	What is the likely place of afatinib in the treatment pathway of EGFR mutation positive locally advanced or metastatic NSCLC? Due to toxicity, we would expect its use to be mainly in 2L or later lines for high performance status patients who are able to tolerate afatinib. Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Performance status 0-1. This group are more likely to tolerate afatinib.	Comment noted. The marketing authorisation for afatinib is yet to be confirmed and so the line of treatment it will be indicated for is unknown. NICE will only appraise this technology within its licensed indication. The workshop attendees did not consider that the evidence

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			for Afatinib based on performance status would be sufficient to support subgroup recommendations.
	The Royal College of Nursing	and it may take less time to administer making a capacity benefit	Comment noted.
Additional comments on the draft scope	Boehringer Ingelheim	No additional comments.	Comment noted.
	Royal College of Pathologists	The appraisal will need to take into account the cost of identifying patients with EGFR mutant tumours.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group
Marie Curie Cancer Care
National Lung Cancer Forum for Nurses
Department of Health
Medicines and Healthcare products Regulatory Agency

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add NHS England	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. NHS England has been added to the matrix of consultees and commentators under 'consultee other.'

2.	Add Health Research Authority	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Health Research Authority has been added to the matrix of consultees and commentators under 'research groups.'
3.	Add NHS Slough CCG	NICE Secretariat		Added	Our process requires the involvement of two CCG/LHBs. NHS Slough CCG has been added to the matrix as a consultee.
4.	Add NHS West Lancashire CCG	NICE Secretariat		Added	Our process requires the involvement of two CCG/LHBs. NHS West Lancashire CCG has been added to the matrix as a consultee.