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Erlotinib for the treatment of non-small-cell lung cancer

**This guidance was developed using the
single technology appraisal process**

NICE technology appraisal guidance 162 Erlotinib for the treatment of non-small-cell lung cancer

Ordering information

You can download the following documents from www.nice.org.uk/TA162

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with non-small-cell lung cancer and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1737 (quick reference guide)
- N1738 ('Understanding NICE guidance').

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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1 Guidance

- 1.1 Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel.
- 1.2 The decision to use erlotinib or docetaxel (as outlined in section 1.1) should be made after a discussion between the responsible clinician and the individual about the potential benefits and adverse effects of each treatment.
- 1.3 Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.
- 1.4 People currently receiving treatment with erlotinib, but for whom treatment would not be recommended according to section 1.3, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Erlotinib (Tarceva, Roche Products) is an orally active inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It is licensed for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. For further information see the summary of product characteristics (SPC).
- 2.2 Side effects of erlotinib treatment include diarrhoea, rash, anorexia, gastrointestinal bleeding, liver-function test abnormalities and

keratitis. For full details of side effects and contraindications, see the SPC.

- 2.3 Erlotinib is given orally at a recommended dose of 150 mg/day. The normal acquisition cost of a pack of 30 tablets (150 mg strength) is £1631.53 (excluding VAT; 'British national formulary' [BNF] 55th edition). The typical drug cost for a course of treatment is £6800 (assuming treatment duration of 125 days and no drug wastage). Costs may vary in different settings because of negotiated procurement discounts. Please see section 3.20 for details of the manufacturer's arrangement for the provision of erlotinib on a discounted basis.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of erlotinib and a review of this submission by the Evidence Review Group (ERG; appendix B). The Committee further considered evidence submitted by consultees and commentators, as requested by the Institute after the appeal, and further evidence provided by the manufacturer on the overall treatment costs of erlotinib to the NHS in England and Wales.

Erlotinib compared with docetaxel

- 3.1 The manufacturer's initial submission focused on a comparison of erlotinib with intravenously delivered docetaxel. The manufacturer noted that docetaxel is the most appropriate comparator because it is the standard treatment option for patients for whom one chemotherapy regimen has failed and who are fit for further chemotherapy. The clinical outcomes examined were overall survival, progression-free survival, tumour response rate, severity of key lung-cancer symptoms, physical functioning, global quality of life and treatment-related adverse events.

- 3.2 The manufacturer identified one trial (BR21, n = 731) comparing erlotinib with placebo/best supportive care (BSC), but did not identify any clinical trials that directly compared erlotinib with docetaxel. An unadjusted indirect comparison of absolute values for these two interventions was therefore reported as a summary of clinical effectiveness. The BR21 trial showed that median overall survival was longer in the erlotinib group (6.7 months, 95% confidence interval [CI] 5.5 to 7.8) than in the placebo group (4.7 months, 95% CI 4.1 to 6.3). The unstratified hazard ratio for death in the erlotinib arm, estimated from a univariate Cox regression model, was 0.76 (95% CI 0.64 to 0.91) relative to placebo.
- 3.3 The manufacturer identified 11 trials in which docetaxel was compared with a number of other treatments. Two of these trials were selected for indirect comparison; TAX317 (n = 204), which compared docetaxel with BSC, and JMEI (referred to as Hanna et al [2004] in the manufacturer's submission, n = 484), which compared docetaxel with pemetrexed. Using absolute survival benefits, the indirect comparison derived a mean overall survival of 9.5 months for erlotinib (BR21) and 8.89 months for docetaxel (TAX317). The manufacturer suggested this could be an underestimate for erlotinib because 23% of patients in BR21 were still alive at the end of the trial. Mean progression-free survival data were not available for TAX317. The manufacturer therefore considered that progression-free survival was best represented by mean treatment duration rather than median progression-free survival. Mean treatment duration was 125 days for erlotinib (BR21) and 101 days for docetaxel (TAX317). The manufacturer concluded that erlotinib was, at minimum, equivalent to docetaxel in terms of overall survival, with a longer period of progression-free survival for erlotinib than for docetaxel. The manufacturer also stated that differences in patient populations in the BR21 and docetaxel trials could have biased the results of the indirect comparison in favour of

docetaxel because of the proportion of patients with poor performance status who had received more than one prior chemotherapy regimen.

- 3.4 The manufacturer presented evidence on the adverse events experienced during treatment with erlotinib and docetaxel, based on an indirect comparison of the data from BR21 and a weighted average of adverse events from all 11 docetaxel trials. In patients receiving docetaxel, 42.9% experienced neutropenia (grades 3 and 4) and 6.6% had febrile neutropenia. In the JMEI study it was reported that 19.2% of patients were treated with granulocyte colony-stimulating factor (G-CSF) to prevent severe neutropenia. In the same study, 3.4% of patients were hospitalised for febrile neutropenia. Alopecia was reported in 41.3% of patients receiving docetaxel. No patients receiving erlotinib experienced febrile neutropenia or alopecia. Erlotinib was associated with higher levels of rash/dermatological problems (75%) and diarrhoea (54%) than docetaxel (9.3% and 22.8%, respectively).
- 3.5 In the BR21 trial, treatment with erlotinib led to a statistically significant increase in time to deterioration in symptoms of NSCLC (cough, dyspnoea and pain) compared with placebo. The manufacturer also indicated that the oral delivery of erlotinib would have a positive impact on patients' quality of life because of the potential for home-based administration.
- 3.6 The manufacturer presented an economic analysis of the cost effectiveness of erlotinib compared with docetaxel. The analysis was based on a three-stage Markov model, with the following health states: progression-free survival, disease progression and death. Equivalent survival between erlotinib and docetaxel was assumed in the analysis. Mean overall survival was assumed to be 9.03 months for both erlotinib and docetaxel based on data from the erlotinib arm of BR21 (n = 488), which compared erlotinib and placebo. Mean treatment duration from BR21 and TAX317 was

used to represent progression-free survival for erlotinib and docetaxel, respectively. Data on adverse events were taken from BR21 for erlotinib and TAX317 for docetaxel. The cost of erlotinib was based on the list price in the BNF (55th edition).

- 3.7 The manufacturer's base-case analysis resulted in erlotinib dominating docetaxel (that is, it was less costly and more effective). The manufacturer's probabilistic sensitivity analysis resulted in a maximum incremental cost-effectiveness ratio (ICER) of approximately £8000 per quality-adjusted life year (QALY) gained and a probability of 68% that the ICER was less than £30,000 per QALY gained.
- 3.8 The ERG report concentrated on the following key issues:
- interpretation of the erlotinib and docetaxel survival curves
 - estimation of progression-free survival
 - health-related utility
 - costs.
- 3.9 By re-examining the survival curves, the ERG calculated that, using either an area under the curve or exponential curve-fitting analysis, the mean overall survival could vary from 8.6 to 9.9 months for erlotinib and from 9.5 to 11.2 months for docetaxel.
- 3.10 The ERG expressed concerns about the approach used by the manufacturer to estimate progression-free survival. The manufacturer used mean treatment duration as a surrogate measure because mean progression-free survival was not reported in TAX317. Mean treatment duration was 101 days (3.3 months) for docetaxel (TAX317 trial) and 125 days (4.1 months) for erlotinib (BR21 trial). However, the ERG noted that the median progression-free survival was 2.9 months in the docetaxel arm of the JMEI trial and 2.2 months in the erlotinib arm of the BR21 trial. It also noted that median time to progression was 2.5 months in the docetaxel arm of the TAX317 trial.

- 3.11 The ERG reviewed the method used by the manufacturer to derive health-related utility estimates. The ERG stated that the estimates were inappropriate as they were obtained using a visual analogue scale, which was not adjusted to reflect death as having a zero utility, and were therefore not suitable for calculating QALYs. Incorporating the ERG's health-related utility estimates into the manufacturer's model reduced the final QALY gain for erlotinib from 0.0304 to 0.0182, compared with docetaxel.
- 3.12 The ERG also noted concerns over the costs of drug acquisition, administration and monitoring for both drugs, along with the calculation of costs attributable to the adverse events associated with docetaxel. The ERG used the BNF list price for all its exploratory analyses.
- 3.13 Incorporating these cost and health-related utility changes, the ERG noted that the ICER would increase to approximately £52,100 per QALY gained. Additional exploratory analyses conducted by the ERG showed that the ICER ranged from £31,300 to £70,400 per QALY gained depending upon the choice of health-related utility measure, the acquisition cost of docetaxel and the impact of reducing the number of cycles of chemotherapy. When also taking into account uncertainties surrounding the data on overall survival and progression-free survival, the ERG noted the possibility that docetaxel would dominate erlotinib (that is, be less costly and more effective).
- 3.14 The rate of febrile neutropenia used in the manufacturer's model was 1.8% based on data from TAX317. Evidence from other docetaxel trials in NSCLC indicated that the rate could vary between 2% and 13%. The Institute requested information from consultees and commentators on the rate of febrile neutropenia. Three random effects meta-analyses were submitted, which produced estimates of 6.5% (95% CI 1.6 to 6.4), 10% (95% CI 3 to 23) and 5.9% (95% CI 3.9 to 8.3). Audit data were presented from

two hospitals, which resulted in estimates of 8.9% and 15%. The Institute instructed its decision support unit (DSU) to undertake a review of the incidence of febrile neutropenia. A random-effects meta-analysis conducted by the DSU, which combined 13 docetaxel trials, resulted in an expected rate of febrile neutropenia of 5.95% (95% CI 4.22 to 8.31).

- 3.15 The manufacturer's model assumed that patients experiencing febrile neutropenia would have an average of 2.4 febrile neutropenic events. This estimate was based on clinical opinion. The DSU reported evidence from a clinical trial in small-cell lung cancer in which there were 1.4 febrile neutropenic events per person.
- 3.16 The manufacturer and a clinical specialist provided estimates of the cost of treating febrile neutropenia. The manufacturer calculated a cost of £4741 per event based on a health resource group tariff cost plus the cost of G-CSF to treat and prevent febrile neutropenia. The clinical specialist included the cost of antibiotics, bed days and G-CSF to estimate a cost of £5616. Both these estimates assumed that all patients experiencing febrile neutropenia would receive G-CSF. The DSU identified evidence from clinicians and NHS trusts that stated that G-CSF is rarely used in the treatment of febrile neutropenia associated with docetaxel. The DSU also noted that clinical guidelines recommend the use of G-CSF only in high-risk patients. The DSU calculated a cost of £2286 per event based on the majority of patients being treated as inpatients, and some patients being treated with oral antibiotics and early hospital discharge.
- 3.17 The DSU and the manufacturer presented cost-effectiveness estimates using the calculations for the rate and cost of febrile neutropenia. The manufacturer presented incremental cost per QALY gained estimates assuming a 6.5% rate of febrile neutropenia and a cost of £4741 per event, which resulted in an

ICER of £22,583 per QALY gained. When the rate was increased by the manufacturer to 10%, the ICER changed to £7381 per QALY gained. Using 5.95% as the rate of febrile neutropenia, 1.4 for the average number of febrile neutropenic events and a cost of £2286 per event, the DSU's calculations resulted in a reduction in the incremental cost of approximately £18 and an increase of 0.001 in the incremental QALY. The result was a minimum ICER of £48,000 per QALY gained, based on the assumptions that led to the ERG's original estimate of £52,100 per QALY gained (see section 3.13).

- 3.18 During the course of the appraisal, the manufacturer presented a network meta-analysis to re-estimate relative overall survival with erlotinib and docetaxel. The meta-analysis incorporated evidence from a range of randomised controlled trials (RCTs) that included two of the following treatments: erlotinib, docetaxel, pemetrexed, gefitinib and placebo/BSC. The analysis resulted in a calculated hazard ratio of 0.845 (95% CI 0.6 to 1.15) for overall survival for erlotinib compared with docetaxel. The manufacturer concluded that this reinforced the conclusion that erlotinib is at least equivalent to docetaxel.
- 3.19 During the course of the appraisal the manufacturer also submitted a new estimate of the cost of administering docetaxel treatment (£299 based on a chemotherapy and respiratory system primary diagnosis code in the payment-by-results tariff). When this was applied, the ERG's amended lowest ICER estimate fell from £52,098 to £5897 per QALY gained. In a critique of the new data, the DSU stated that the costings were inappropriate as they were based on a day-case code. The DSU noted that docetaxel infusions usually last approximately 1 hour and therefore outpatient attendance was more appropriate.
- 3.20 The manufacturer noted the Committee's concerns over the incremental survival benefit and costs of erlotinib compared with docetaxel. Consequently the manufacturer proposed an

arrangement that would involve the provision of erlotinib to the NHS in England and Wales on a discounted basis which would have the effect of equalising the total costs of treatment with erlotinib (including administration, adverse events and monitoring costs) with those of docetaxel. The manufacturer outlined the arrangement as follows. The manufacturer assumed that docetaxel is associated with a drug acquisition cost of £5022 (based on a mean 4.82 cycles of treatment), drug administration costs of £1064, adverse event costs of £392 and G-CSF costs of £236, leading to a total cost of treatment of £6714. The manufacturer then subtracted from £6714 erlotinib's drug administration cost (£473) and adverse event management cost (£113), as outlined in the ERG report, resulting in a new acquisition cost of erlotinib of £6128. The Department of Health in England and the Department of Health and Social Services in Wales accepted the arrangement for consideration by NICE.

Erlotinib compared with best supportive care

- 3.21 Following a request from the Committee, the manufacturer carried out two further cost-effectiveness analyses on two subgroups in the BR21 trial: patients receiving second-line treatment (for whom docetaxel is unsuitable) and patients receiving third-line treatment after docetaxel therapy. Both of these analyses were comparisons of erlotinib with BSC. The subgroups were defined by performance score and treatment line. The manufacturer extrapolated survival data for patients receiving erlotinib as a third-line treatment because 23% of patients were still alive at the end of the trial period. In the second-line group, all patients had died before completion of BR21 and therefore the data were not extrapolated beyond the end of the trial period. In addition, the manufacturer applied other amendments to the model, in particular the approach to health-related utility estimates suggested by the ERG and drug wastage and compliance data based on patient-level data from the BR21 trial. The price of erlotinib and docetaxel was based on the

BNF list price. The manufacturer's analysis concluded that the ICER for the second-line group was £78,300 per QALY gained and for the third-line group was £54,200 per QALY gained.

- 3.22 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TA162

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of erlotinib for the treatment of NSCLC, having considered evidence on the nature of the condition and the value placed on the benefits of erlotinib by people with NSCLC, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.2 The Committee noted that patients may prefer erlotinib treatment to docetaxel because it is orally administered and they would therefore need to spend less time in hospital receiving treatment. The clinical specialists and patient experts emphasised erlotinib's favourable toxicity profile, with fewer serious adverse events reported during treatment with erlotinib than with docetaxel. The Committee also heard from the specialists that erlotinib was an important development, was well tolerated by patients, and offered a line of treatment in the late stages of the disease when previously no options were available. The Committee was aware that the survival benefit of erlotinib over no treatment (demonstrated in the BR21 trial) is contributing to patients' expectations that erlotinib may be used in circumstances where no other treatment is available.

Erlotinib compared with best supportive care

- 4.3 The Committee noted the clinical and patient experts' views that erlotinib is a potential breakthrough in delaying progression of

NSCLC in patients for whom no other treatment is available. The Committee therefore considered the use of erlotinib for patients in whom docetaxel is unsuitable or as third-line treatment after the failure of docetaxel. The Committee heard from clinical specialists that it was in these circumstances that erlotinib may be most beneficial given its tolerability and the lack of treatment options available.

- 4.4 The Committee considered the evidence submitted by the manufacturer for both of these groups of patients. It noted that the manufacturer's ICER of £78,300 per QALY gained for second-line use when docetaxel is unsuitable, and £54,200 per QALY gained for third-line use, were considerably higher than acceptable. Given these data, the Committee concluded that erlotinib was not a cost-effective use of NHS resources for the treatment of patients with locally advanced or metastatic NSCLC for whom docetaxel is unsuitable as second-line treatment or following docetaxel as second-line treatment for patients who would normally receive BSC.

Erlotinib compared with docetaxel

- 4.5 The Committee considered the assumption of equivalence in absolute overall survival between erlotinib and docetaxel proposed by the manufacturer, and heard from clinical specialists that, in their view, erlotinib provides a similar survival benefit to docetaxel. It considered all the survival estimates for erlotinib compared with docetaxel, including the unadjusted indirect comparison provided in the manufacturer's original submission and the network meta-analysis presented later in the course of the appraisal. The Committee was concerned about the comparability of the trials used in the unadjusted indirect comparison of absolute survival benefit in terms of performance status, treatment stage and the effectiveness of BSC given that the TAX317 trial pre-dated the BR21 trial significantly. The Committee considered the

manufacturer's assertion that the differences in case-mix between the BR21 and TAX317 trials biased the clinical evidence in favour of docetaxel. However, the Committee concluded that any differences in characteristics between the trials could also result in a bias in the opposite direction. The Committee noted that the patients included in the trials may not accurately reflect the population of patients with NSCLC. In particular, it noted that the BR21 trial included a higher proportion of non-smokers than would be expected in clinical practice.

- 4.6 The Committee considered the network meta-analysis presented by the manufacturer and concluded that it was not robust for several reasons. Firstly, and most significantly, it considered that differences in patient characteristics between trial populations were likely to have had an impact on the relative efficacy of the treatments. Indeed, the manufacturer had previously argued against comparing the efficacy of docetaxel and erlotinib through common comparators. Secondly, it noted that only a selection of trials had been used in the network meta-analysis, and that including gefitinib was outside the manufacturer's inclusion criteria, which stated that only treatments with marketing authorisations in the UK should be included. In addition, a full systematic review should have been conducted including an assessment of the heterogeneity within the selected trials. The Committee also noted that the most heavily weighted parts of the network meta-analysis came from two gefitinib trials, which were key to strengthening the case for erlotinib relative to docetaxel. The Committee noted that the overall survival with gefitinib in the larger trial included in the network meta-analysis was not statistically significantly different from overall survival with placebo. The Committee noted that this was inconsistent with the data from the other trial included in the network meta-analysis that showed gefitinib to be equivalent to docetaxel in overall survival benefit. The Committee considered that there was great uncertainty over the relevance of the gefitinib

trials in informing the indirect comparison between erlotinib and docetaxel. Overall, the Committee concluded that the network meta-analysis provided by the manufacturer was unlikely to have produced reliable estimates of the effectiveness of erlotinib compared with docetaxel.

- 4.7 The Committee considered the re-analysis of the BR21 and TAX317 trials by the ERG in which they showed that docetaxel could provide longer mean overall survival than erlotinib. It noted that the ERG expressed concern about the manufacturer's assumption of equivalent survival with erlotinib and docetaxel. The Committee considered the ERG's re-examination of the survival data, which showed that absolute survival benefits ranged from 8.6 to 9.9 months for erlotinib, and from 9.5 to 11.2 months for docetaxel, depending on the method of calculation used. The Committee noted that the manufacturer had expressed concern about the curve-fitting method that was applied for the re-analysis by the ERG when one trial, BR21, had long-term survivors and the other, TAX317, did not. The Committee then explored the relative mean survival gain from erlotinib and docetaxel compared with BSC in the BR21 and TAX317 trials. It noted that the relative survival benefit versus BSC was 2.07 months for erlotinib in BR21 and 3.73 months for docetaxel using the final TAX317 data.
- 4.8 Taking all the survival estimates for erlotinib compared with docetaxel into consideration, the Committee was not persuaded that erlotinib had a proven equivalent survival benefit when compared with docetaxel. The Committee accepted the possibility that it would be reasonable to conclude, based on current evidence, that erlotinib shows a lower survival benefit compared with docetaxel.
- 4.9 The Committee further discussed the use of treatment duration as a surrogate for progression-free survival, and considered the approach taken by the manufacturer to be inappropriate. It noted

that the relative benefit assumed for erlotinib, when using mean treatment duration as a surrogate for progression-free survival, was reversed when median time to progression for docetaxel was used instead. This conclusion was reinforced when the progression-free survival data from the JME1 trial were considered. Therefore, the Committee was not persuaded that erlotinib was proven to provide a longer duration of progression-free survival than docetaxel. The Committee considered that the opposite was more likely based on current evidence.

- 4.10 The Committee discussed the adverse events affecting patients who were treated with each drug, particularly the lack of alopecia, neutropenia and febrile neutropenia with erlotinib. It noted that these adverse events had been reflected in the difference between the health-related utility estimates for erlotinib and docetaxel used in the manufacturer's economic model. The Committee discussed evidence presented by consultees, commentators and the DSU on the rate, number of events and cost of febrile neutropenia with docetaxel. Of all the estimates presented, the Committee considered that those using meta-analyses were the most robust. The Committee considered the DSU estimate of 5.95% for febrile neutropenia was the most realistic given the transparency of the data and methods used in the selected trials, although the Committee noted that the manufacturer's final alternative estimate of 6.5% would not make a material difference to docetaxel's effectiveness or cost calculations. The Committee considered that the two meta-analyses provided by the manufacturer were less robust because they included inappropriate adjustments and included unpublished trials with insufficient details about the populations studied. It noted the evidence for the average number of events of febrile neutropenia per patient and that the DSU estimate of 1.4 was based on data from a study of small-cell lung cancer patients. The Committee considered that this could be generalised to patients with NSCLC and was to be preferred over

the original estimate of 2.4 because it was based on empirical evidence.

- 4.11 Having accepted the likelihood that erlotinib could not reasonably be considered to have an overall survival benefit when compared with docetaxel, and that a progression-free survival benefit with docetaxel was more probable, the Committee considered that the benefits of oral administration and the adverse event profile of erlotinib were not sufficient to lead to a net benefit compared with docetaxel, in patients for whom docetaxel was an option.
- 4.12 Nevertheless the Committee was mindful that while the difference in benefit between docetaxel and erlotinib was uncertain in the absence of direct comparisons, erlotinib could be acceptable if the total costs of treatment were lower or equal to those of docetaxel. It therefore considered the cost profiles of the two drugs, including the costs related to the drugs' adverse events.
- 4.13 The Committee noted all the key elements of the cost of treatment. Firstly, the difference in drug acquisition costs (using the BNF list price) between erlotinib and docetaxel was in excess of £2100 per patient, with erlotinib being the more expensive. Secondly, the Committee discussed whether administration of docetaxel should be considered as an outpatient appointment or on a day-case basis. Given the resource use and short infusion time of docetaxel, the Committee concluded that an extended outpatient appointment most appropriately reflected current practice. It concluded that the costs of administering docetaxel were most reasonably considered to be between an outpatient costing and a day-case costing. The Committee noted that the most appropriate NHS reference cost (SB12Z) puts it in this range (at £170 per case). The Committee discussed whether two outpatient visits would be required to administer docetaxel. It accepted that there would be variation across the country, but assumed two visits for all patients would overestimate the cost. It concluded that one visit, costed between

an outpatient and a day-case cost, would best represent the cost of delivering docetaxel. This results in an administration cost difference between the drugs of approximately £600, with docetaxel the more expensive. Thirdly, the Committee discussed the cost of febrile neutropenia and the estimates provided. The Committee considered that the estimates based on the payment-by-results tariff were not appropriate as these were based on a broad range of different treatments. It noted that the estimate provided by the DSU was specifically for treating febrile neutropenia and was based on empirical evidence. The Committee therefore concluded that the cost estimate provided by the DSU was the most appropriate, but allowed for the manufacturer's concern that the rate of febrile neutropenia as a result of docetaxel use could rise from 5.95% to 6.5%. At a rate of 5.95% and with 1.4 episodes per affected patient, the resulting cost difference between docetaxel and erlotinib narrows by a further £280. The Committee accepted some use of G-CSF at the manufacturer's estimate of £1388 per febrile neutropenic event and explored scenarios where 17% of all patients received G-CSF and those where only patients with febrile neutropenia received G-CSF. In both cases erlotinib remained more expensive by approximately £1000 per patient.

- 4.14 The Committee considered the effect of equalising the overall treatment costs between erlotinib and docetaxel. The Committee accepted that it was difficult to derive conclusions on the basis of the indirect comparisons presented and that uncertainty remained about the difference in effectiveness between erlotinib and docetaxel. The Committee considered that, with the arrangement of equalising the overall treatment costs, any remaining differences between the treatments would be found in effectiveness and toxicity alone. A discussion of the benefits and adverse effects of both treatments should form part of discussions between clinicians and individual patients who would use this information to make informed decisions about the most appropriate treatment. The

Committee concluded that in patients who were eligible for docetaxel, erlotinib should be considered as a treatment option under the arrangements of equal overall treatment costs.

Subgroups

- 4.15 The Committee also considered potential subgroups towards whom erlotinib treatment could be targeted. The clinical specialists reported that the patients most likely to benefit from erlotinib were female non-smokers of South Asian ethnicity, presenting with adenocarcinoma. The Committee noted that erlotinib might provide a superior response in a selected group of patients; however, the current evidence base remains too weak to infer effectiveness or cost effectiveness in this subgroup. A further possible subgroup, based on EGFR status, was also discussed. The clinical specialists stated that although the link between tumours expressing EGFR and the efficacy of erlotinib was not yet conclusively proven, this could be another identifier of a subgroup of patients towards whom treatment could be specifically targeted. The Committee noted that EGFR status and other tumour biochemical markers are being explored in current research, which will advance the understanding of the mechanism of action of erlotinib. However, the Committee considered the current evidence base to be insufficient to allow conclusions to be reached about the targeting of specific subgroups for erlotinib treatment.

Summary

- 4.16 The Committee concluded that erlotinib could not be considered a cost-effective use of NHS resources when compared with BSC. The Committee concluded that it could recommend erlotinib only in patients eligible for docetaxel treatment and only when the overall treatment costs of the two treatments were equalised and after a discussion between the responsible clinician and patient about the potential benefits and adverse effects of each treatment.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA162).
- Audit support for monitoring local practice.
 - A costing statement explaining the resource impact of this guidance.

6 Recommendations for further research

- 6.1 NICE awaits the results of ongoing trials comparing erlotinib with docetaxel.

6.2 NICE recommends further research into subgroups for whom erlotinib may provide greater benefit.

7 Related NICE guidance

Published

Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). NICE technology appraisal guidance 148 (2008) Available from www.nice.org.uk/TA148

Pemetrexed for the treatment of malignant pleural mesothelioma. NICE technology appraisal guidance 135 (2008). Available from www.nice.org.uk/TA135

Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 (2007). Available from www.nice.org.uk/TA124

Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 24 (2005). Available from www.nice.org.uk/CG024

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Cetuximab for the treatment of advanced non-small-cell lung cancer. NICE technology appraisal guidance (publication expected July 2009).
- Gefitinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance (publication expected November 2009).

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology will be considered for review in June 2010. The Committee await the results of trials directly comparing erlotinib and docetaxel. The Institute would particularly welcome comment on this proposed date.

Andrew Dillon
Chief Executive
November 2008

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and a vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Chesterfield PCT

Dr Carol Campbell

Senior Lecturer, University of Teesside

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Professor David Chadwick

Professor of Neurology, Liverpool University

Dr Peter Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology,
Merseyside

Ms Jude Cohen

Chief Executive, Women's Nationwide Cancer Control Campaign

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, Nottingham University

Mrs Eleanor Grey

Lay member

Dr Dyfrig Hughes

Reader in Pharmacoeconomics, Centre for Economics and Policy in Health,
Bangor University

Dr Catherine Jackson

Professor of General Practice, St Andrews University

Dr Peter Jackson

Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust

Professor Peter Jones

Pro Vice Chancellor for Research and Enterprise, Keele University

Dr Damien Longson

Consultant in Liaison Psychiatry, North Manchester General Hospital

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag Ltd

Dr Philip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Mark Sculpher

Professor of Health Economics, University of York

Professor Andrew Stevens

Chair of Appraisal Committee C

Dr Cathryn Thomas

Senior Lecturer, Department of Primary Care and General Practice

Mr William Turner

Consultant Urologist, Addenbrookes Hospital

B ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Prashanth Kandaswamy

Technical Lead

Louise Longworth and Zoe Charles

Technical Advisers

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG):
- Bagust A, Boland A, Dundar Y et al, Erlotinib for the treatment of relapsed non-small-cell lung cancer, September 2006.
- B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on erlotinib by providing a written statement to the Committee. Organisations listed in I, II and III were invited to submit further evidence as a result of the appeal decision. Organisations listed in I and II had the opportunity to appeal against the final appraisal determination.
- I Manufacturer/sponsor:
- Roche Products
- II Professional/specialist and patient/carer groups:
- British Oncology Pharmacy Association (BOPA)
 - British Thoracic Oncology Group
 - British Thoracic Society
 - Cancerbackup
 - Cancer Research UK
 - Roy Castle Lung Cancer Foundation
 - Royal College of General Practitioners
 - Royal College of Nursing
 - Royal College of Pathologists
 - Royal College of Physicians of Edinburgh
 - Royal College of Physicians, Medical Oncology Joint Special Committee
 - Tenovus Cancer Information Centre
 - Welsh Assembly Government

III Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Eli Lilly and Company Ltd
- Institute of Cancer Research
- MRC CTU – Lung Cancer and Mesothelioma Group
- National Collaborating Centre for Cancer
- NHS Quality Improvement Scotland
- sanofi-aventis

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on erlotinib by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Jesme Baird, Director of Patient Care, nominated by the Roy Castle Lung Cancer Foundation – patient expert
- Professor David R Ferry, Medical Oncologist, New Cross Hospital, Wolverhampton, nominated by the Royal College of Physicians – clinical specialist
- Dr Mary O'Brien, Consultant Medical Oncologist, Institute of Cancer Research, nominated by the Institute of Cancer Research – clinical specialist
- Dr Elizabeth Sawicka, Consultant, Princess Royal University Hospital, nominated by The British Thoracic Society – clinical specialist