NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pemetrexed in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from www.nice.org.uk

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using pemetrexed in the NHS in England and Wales.

For further details, see the 'Guide to the technology appraisal process' (available at www.nice.org.uk).

The key dates for this appraisal are:

Closing date for comments: 11 September 2013

Second Appraisal Committee meeting: 25 September 2013

Details of membership of the Appraisal Committee are given in section 8 and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology for people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.

1.2 People currently receiving pemetrexed as maintenance treatment following induction therapy with pemetrexed and cisplatin should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Pemetrexed (Alimta, Eli Lilly and Company) is a multi-targeted anticancer antifolate agent that disrupts crucial folate-dependent metabolic processes essential for cell replication. Pemetrexed has a marketing authorisation as 'monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy'.

2.2 The summary of product characteristics reports that the most common adverse reactions of pemetrexed are bone marrow suppression manifested as anaemia, neutropenia, leucopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis,

mucositis, and stomatitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The summary of product characteristics states that the recommended dose of pemetrexed is 500 mg/m^2 of body surface area; it is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. To reduce toxicity, patients treated with pemetrexed should also receive folic acid and vitamin B12 supplements. To reduce the incidence and severity of skin reactions, premedication with a corticosteroid is recommended.

2.4 The list price for pemetrexed is £160 for a 100-mg vial and £800 for a 500-mg vial (excluding VAT; 'British national formulary' [BNF] edition 64). Using the manufacturer's estimated average body surface area of 1.79 m^2 the drug cost for each treatment cycle is £1440. Because patients are treated until disease progression or toxicity, the number of cycles varies; in the clinical trial the mean number of cycles given for maintenance was 7.86. Therefore, assuming 8 cycles of treatment, the average total treatment cost is approximately £11,520. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of pemetrexed and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The evidence for the clinical effectiveness of pemetrexed maintenance therapy following prior treatment with pemetrexed plus cisplatin induction therapy was from a single trial: PARAMOUNT. This was an international, multicentre (83 sites

across 16 countries including the UK), double-blind, phase III, randomised trial in patients with stage IIIB or stage IV non-squamous NSCLC whose disease had not progressed after 4 cycles of pemetrexed plus cisplatin induction therapy. Only patients whose disease had a complete or partial response to induction therapy or with stable disease and good Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were randomised to maintenance treatment. Of 939 patients treated with pemetrexed plus cisplatin induction therapy, 539 patients (57.4%) were randomised to receive maintenance treatment with either pemetrexed plus best supportive care (n=359) or placebo plus best supportive care (n=180). Patients in the pemetrexed arm received pemetrexed 500 mg/m^2 on day 1 of the 21-day cycle, administered as an infusion, plus best supportive care. Maintenance therapy was continued until disease progression, unacceptable adverse events, or the patient or physician decided to stop. Patients were followed up until death or study closure. Patients in both arms received concomitant medication with folic acid, vitamin B12 and dexamethasone.

3.2 The median age of patients in PARAMOUNT was 61 years; 58% were men. Most (91%) had stage IV disease. A greater proportion had an ECOG performance status of 1 (67%) than of 0 (32%). Approximately 22% had never smoked. The demographic characteristics of patients in the trial were similar between the 2 groups.

3.3 The primary outcome of PARAMOUNT was median progression-free survival. At the final March 2012 data lock this was 4.44 months (95% confidence interval [CI] 4.11 to 5.65) in the pemetrexed arm compared with 2.76 months (95% CI 2.60 to 3.02) in the placebo arm, an overall median progression-free survival

benefit of 1.68 months. The hazard ratio (HR) for progression was 0.60 (95% CI 0.50 to 0.73, p<0.00001) for pemetrexed compared with placebo.

3.4 Median overall survival, measured from the date of randomisation, was 13.86 months (95% CI 12.75 to 16.03) in the pemetrexed arm compared with 11.01 months in the placebo arm (95% CI 9.95 to 12.52), an overall median survival benefit of 2.85 months. The hazard ratio was 0.78 (95% CI 0.64 to 0.96, p=0.0195) for patients receiving pemetrexed compared with placebo.

3.5 Quality of life was assessed in PARAMOUNT using the EQ-5D questionnaire, completed at 4 time points during the trial. A total of 325 patients in the pemetrexed arm and 165 patients in the placebo arm had data at baseline and at least 1 subsequent measurement during maintenance treatment. No statistically significant differences were observed between the 2 arms. Over 75% of patients in both arms maintained their performance status during the study and there was no statistical difference in change in performance status between the 2 arms.

3.6 Grade 3 or 4 non-laboratory adverse reactions were reported by 11.7% (42/359) of patients in the pemetrexed arm and 4.4% (8/180) of patients in the placebo arm. The most common grade 3 or 4 adverse reactions associated with pemetrexed were fatigue (5.3% [19/359]), anaemia (6.7% [24/359]) and neutropenia (6.1% [22/359]). More patients were hospitalised because of treatment-related adverse reactions in the pemetrexed arm than in the placebo arm (10.9% [39/359] compared with 3.3% [6/180], p=0.003). Overall, more patients on pemetrexed needed transfusions than on placebo (18.4% [66/359] compared with 6.1% [11/180], p<0.001).

3.7 There was no statistically significant difference between the rates of second-line chemotherapy after stopping maintenance treatment with pemetrexed (64.3%) or placebo (71.7%), approximately equal proportions of people having docetaxel or erlotinib in both arms.

Cost effectiveness

3.8 The manufacturer submitted an economic analysis comparing pemetrexed with placebo. The manufacturer's model was a state-transition Markov model with 3 health states: pre-progression, post-progression and death. The transition from pre-progression to post-progression was estimated from progression-free survival; the transition from either pre- or post-progression to death was estimated from overall survival. The economic model used overall survival data, progression-free survival data, treatment discontinuation rates and adverse events from the final data lock (March 2012) from the PARAMOUNT trial. The cycle length of the model was 21 days and the base-case time horizon was 16 years.

3.9 Treatment effectiveness in the model was based on the final data lock (March 2012) with extrapolation of the data to provide survival estimates for the lifetime of the model. Censoring rates in PARAMOUNT were 28.7% (pemetrexed) and 21.7% (placebo) for overall survival and 8.1% (pemetrexed) and 6.7% (placebo) for progression-free survival. The manufacturer explored 6 alternative parametric distributions to extrapolate the data: exponential, Weibull, log-logistic, log-normal, Gompertz and gamma. The manufacturer concluded that, based on consideration of Akaike's Information Criterion, Bayesian Information Criterion and Cox-Snell residual statistics, visual fit and plausibility of survival estimate, the gamma distribution was the most appropriate for both overall survival and progression-free survival. Projective models were fitted to the survival data, and, for overall survival, applied from the point

where approximately 20% of patients remained at risk of death in each arm; this was at cycle 37 in the pemetrexed arm and cycle 31 in the placebo arm. The mean overall survival resulting from the manufacturer's economic model was 20.46 months for pemetrexed and 16.24 months for placebo, giving a gain of 4.21 months for pemetrexed.

3.10 The cost of pemetrexed was based on the licensed dose (500 mg/m^2) and a mean body surface area of 1.79 m^2 (the average body surface area of UK patients with lung cancer weighted by the gender mix in PARAMOUNT). The cost of pemetrexed included drug wastage for part-used vials. NHS reference costs were used to estimate pemetrexed delivery costs. The cost of concomitant medications to be taken with pemetrexed, such as vitamin B12, folic acid and dexamethasone, was assumed to be contained within the relevant chemotherapy tariff. Costs were also included for the additional monitoring associated with maintenance treatment: over the mean 24 week duration of pemetrexed maintenance treatment, patients in the model needed 1 additional consultant oncology consultation, 3% had additional CT scans and 58% had additional chest radiographs. The cost of treating adverse events included all grade 3 and 4 adverse events occurring at a rate of over 2%, plus costs for treating nausea and vomiting. The costs of best supportive care and terminal care were based on figures from Pemetrexed for the maintenance treatment of non-small-cell lung cancer (NICE technology appraisal guidance 190) and inflated to 2011 prices.

3.11 Patients in PARAMOUNT were asked to rate their present health condition using the EQ-5D instrument. The manufacturer noted that the trial data did not provide values suitable for the pre- and post-progression health states, therefore a mixed regression analysis

was carried out to estimate these values. The analysis considered covariates of treatment, disease progression and time before death, but was not adjusted for variation in baseline characteristics (the unadjusted model). Utility values for each health state were calculated as the sum of a constant utility value of 0.3369 plus the appropriate coefficient for the health state, as defined by time before death and progression status. For patients receiving pemetrexed, a decrement of −0.0248 was included in the calculation. The resulting utility values in the unadjusted model ranged from 0.3369 for the lowest health state (patients in the post-progression health state receiving either treatment, who were 0 to 2 cycles prior to death) to 0.7758 for the best health state (patients in the pre-progression health state receiving placebo treatment, who were more than 6 cycles of treatment prior to death). In addition, the manufacturer's submission included alternative options for assigning health state utility values. These options included an extended regression model (the adjusted utility model) in which additional covariates of ECOG status, response to induction therapy and historical illness were included; and utility values from a publication by Nafees et al. (2008) that had been used in NICE technology appraisals 190, 192 (Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer) and 227 (Erlotinib monotherapy for the maintenance treatment of non-small-cell-lung cancer) and were based on a population of people with NSCLC that had progressed.

3.12 In the manufacturer's base case, the incremental cost-effectiveness ratio (ICER) for pemetrexed compared with placebo was £47,576 per quality-adjusted life year (QALY) gained (incremental cost of £12,153 and incremental benefit of 0.2554 QALYs).

3.13 The manufacturer carried out several one-way sensitivity analyses to identify which variables were key drivers of the costs and health benefits in the model, and to explore uncertainty around the ICER. The manufacturer's deterministic sensitivity analyses showed that the modelling using 'fully parametric overall survival with observed progression-free survival and treatment discontinuation' had the greatest impact on the base-case ICER, increasing it to £58,091 per QALY gained. The manufacturer's probabilistic sensitivity analysis suggested that there was a 54% probability of pemetrexed plus best supportive care being cost effective if the maximum acceptable ICER was £50,000 per QALY gained.

Evidence Review Group comments

3.14 The ERG considered PARAMOUNT to be well designed and well conducted, with a patient population predominantly from European centres. However, the ERG noted that the patients in the trial were generally younger and fitter than patients treated for NSCLC in England and Wales. They were generally of a higher performance status and more patients had stage IV disease than would be expected in UK clinical practice. The ERG also commented that a lower proportion in the trial had ever smoked. The ERG also questioned the number of cycles of maintenance pemetrexed treatment likely to be used in clinical practice, suggesting that more than 6 may not be common practice in England and Wales.

3.15 Regarding model design, the ERG noted that the core of the model appeared to be largely sound. However the ERG raised concerns relating to:

- the estimation of cost, resource use and utility parameters in the model

- a case-mix adjusted version of the model, which had been developed by the manufacturer but had not been used
- the point from which the manufacturer projected overall survival from the survival data
- the estimation of overall survival, which appeared to result in a post-progression benefit for pemetrexed that was not apparent in the PARAMOUNT data.

3.16 Regarding the estimation of cost and resource use in the model, the ERG questioned 7 parameters within the manufacturer's base-case analysis that it believed had resulted in inaccurate estimation. These were: the method used for estimating pemetrexed costs according to average body surface area, the use of a half-cycle correction for the drug cost of pemetrexed, costs associated with post-progression chemotherapy, the method of calculating the cost of docetaxel in second-line treatment, omission of concomitant medication costs, progression-free survival monitoring costs and terminal care costs. Regarding the estimation of health state utility values, the ERG commented that the manufacturer had not justified the use of the unadjusted model in preference to the adjusted utility model (see section 3.11), despite the results from the adjusted model appearing to be more closely related to the observed trial data than those from the unadjusted model.

3.17 The ERG noted that the manufacturer had developed adjusted statistical models for projecting overall survival and progression-free survival beyond the trial data, in which the influence of baseline covariates of patient characteristics in PARAMOUNT was accounted for. The ERG stated that the covariates exhibited statistically significant parameter values indicating significantly superior model fit compared with the unadjusted models. However, the ERG noted that the manufacturer used the unadjusted models

in the base case, giving the reason that it was unnecessary to take these factors into account because the randomisation of patients should ensure that all relevant variables are fully balanced within the trial data set. The ERG stated that this would be appropriate when calculating results directly from trial data, but may not be valid in relation to a parametric model fitted to those data. The ERG confirmed that the effect of using the adjusted models would be to increase the base-case ICER by £1991 per QALY gained. The ERG suggested that if the manufacturer's method for projecting survival beyond the observed data is preferred by the Committee, then it would be more appropriate to base the analysis on the adjusted models.

3.18 The ERG raised concerns regarding the choice of time point at which projective modelling took over from observed trial data. The ERG noted that the manufacturer’s model used the time point at which 20% of patients remained at risk of death in the trial, which occurred at cycle 31 in the placebo arm and cycle 37 in the pemetrexed arm. The manufacturer stated that this avoided any potential bias that may occur if the Kaplan-Meier curves were cut at a specific number of cycles for both arms. This method was also chosen by the manufacturer on the basis that it had been adopted by the ERG in NICE technology appraisal guidance 227. However the ERG stated that in that appraisal, maturity referred to the results from the Kaplan-Meier analysis of the data, that is, the proportion of the original cohort estimated to be event free at a particular time point, regardless of the absolute number of individuals not yet censored. The ERG carried out an exploratory analysis using a common survival rate between both arms at thresholds of 15%, 20% and 25% survival. In all cases, the ICER was less favourable to pemetrexed. Using a survival threshold of

20%, the ERG estimated that the ICER would increase by £7360, to £54,936 per QALY gained.

3.19 The ERG questioned why the manufacturer's model resulted in a survival advantage for pemetrexed after disease progression (27% of the undiscounted survival gain for pemetrexed in the manufacturer's model occurred in the post-progression phase). The ERG analysed the post-progression survival data from PARAMOUNT and found that the prognosis for patients in the post-progression phase of both arms was the same. The structure of the model did not allow post-progression survival to be adjusted separately from progression-free survival and overall survival. Therefore, in order to explore the effect on the ICER of taking out the post-progression gain for pemetrexed, the ERG removed the excess QALY gain and made a pro-rata adjustment to post-progression follow-up, with the result that the base-case ICER increased to £54,936 per QALY gained.

3.20 The ERG further explored the manufacturer's approach to survival modelling by re-analysing the overall survival data from the trial. In doing so the ERG found that the manufacturer's gamma model produced a poor fit to the Kaplan-Meier curve. The ERG indicated that this was most pronounced for the placebo arm (which is based on a smaller sample size). In the placebo arm, the ERG stated that the trend was towards steadily increasing underestimation of survival, whereas in the pemetrexed arm the trend was towards steadily increasing overestimation of overall survival. The ERG concluded that the consequence of the manufacturer's approach to projecting overall survival was that differences in expected overall survival are biased in favour of pemetrexed. The ERG suggested that this could explain the source of the apparent gain in post-progression survival in the manufacturer's model. To investigate

the possible causes of this, the ERG fitted an exponential distribution to the observed trial data (instead of the gamma distribution) and found a closer match to the observed survival data in both arms of the trial. Substituting the gamma distribution with the exponential distribution (without any other changes to the manufacturer's base case) had a significant impact on the base-case ICER, increasing it by £14,859 to £62,435 per QALY gained.

3.21 The ERG produced 3 alternative exploratory analyses to be compared with scenario 1, which was the manufacturer's base-case scenario.

- Scenario 2 assumed that all the structures and analyses in the manufacturer's model were appropriate and only formula errors and the 7 parameter values needed amending, as described in section 3.16. This produced an ICER of £58,092 per QALY gained, representing incremental costs of £14,339 for a gain of 0.2468 QALYs.
- Scenario 3 assumed that case-mix adjustments were applied to progression-free survival and overall survival; the survival modelling using a gamma distribution was appropriate; cut-off time points for projections of overall survival were applied in a balanced fashion between the arms of the evaluation; and scenario 2 cost corrections were applied (see sections 3.17 and 3.18). This produced an ICER of £68,810 per QALY gained, representing incremental costs of £14,276 for a gain of 0.2075 QALYs.
- Scenario 4 replaced the single overall survival gamma distribution with an exponential distribution; incorporated the covariate adjusted survival model for progression-free survival; and used the cost corrections from scenario 2. This produced an ICER of £76,344 per QALY gained (representing incremental

costs of £14,242 for a gain of 0.1866 QALYs) and a mean overall survival gain of 3.38 months for pemetrexed compared with best supportive care.

Response to consultation

3.22 In response to consultation the manufacturer submitted a revised base case in which amendments had been made to reflect some of the Committee's preferred assumptions in the appraisal consultation document. These amendments included:

- revised drug cost calculations for pemetrexed and docetaxel
- no half-cycle correction
- no difference in chemotherapy rates after progression
- an increase in the costs of monitoring
- an increase in the cost of terminal care
- a common level of survival in both arms (25%) at which time projective modelling takes over from observed trial data.

3.23 The result of these amendments was to increase the ICER from the base case of £47,576 per QALY gained to a revised base-case ICER of £58,918 per QALY gained (incremental costs of £14,611 for a gain of 0.248 QALYs) for pemetrexed compared with best supportive care. The revised base case did not use the adjusted utility model, asserting that the utility values from this adjusted model were not intuitive because they were higher in the post-progression period than in the pre-progression period. In addition, the revised base case was not amended to include parametric distribution to project survival. The manufacturer considered that the gamma distribution, which resulted in a continued benefit of pemetrexed above best supportive care beyond the treatment period, was appropriate for the survival model. The manufacturer had received clinical expert advice suggesting that pemetrexed

could alter the tumour such that benefit continues beyond progression. In addition, the manufacturer highlighted 2 papers (Stein et al. 2009 and Stein et al. 2011) as evidence to support a hypothesis of biological plausibility for a continuing treatment effect after discontinuation of therapy (using non-pemetrexed treatments) for advanced prostate and renal cell cancers.

3.24 The ERG validated the manufacturer's revised base case and found the changes to have been implemented as described. The ERG clarified that the costs of monitoring included the cost of a CT scan once every 4 cycles (rather than every 8 cycles), and that this appeared in line with the Committee's intentions. The ERG noted that the manufacturer had accepted the principle of the ERG's approach to extrapolation in which a common level of survival was chosen as the point from which to commence overall survival projection (see section 3.18). However, the 25% survival level on the Kaplan-Meier curve was chosen, rather than the 20% survival level as in the ERG exploratory analysis. The impact on the ICER from this amendment was much lower than in the ERG's exploratory analysis (an increase of £1377 compared with £7360 per QALY gained). Accepting that starting the projective modelling at 20% or 25% was subject to individual judgement, the ERG investigated this issue further, and found that at a survival level of 37.2%, the Kaplan-Meier estimate and the overall survival projection model corresponded precisely. Therefore, starting projection at this 37.2% common level of survival was considered by the ERG to eliminate bias between the arms caused by variation at the start of projection.

3.25 The ERG commented on the 2 remaining areas of discrepancy between the manufacturer's revised base case and the Committee's preferred assumptions for the ICER. These were: the

use of utility values from the unadjusted utility model (see section 3.16), and the use of the gamma distribution to project overall survival (see section 3.20). Regarding the use of the unadjusted utility model, the ERG noted from the consultation response that the manufacturer's reason for not using the case-mix adjusted values was that this model produced counterintuitive results (higher utility estimates in the post-progression period than in the pre-progression period). The manufacturer had explained that this was because the model employed a 'cycle' variable to account for changes in utility values as patients move through the cycles. The ERG explained that, in view of this, neither the adjusted nor the unadjusted utility models could be considered robust. Instead, the ERG considered that the Nafees mixed methods model (see section 3.11) that had been used previously in technology appraisals of treatments for non-small-cell-lung cancer: (NICE technology appraisal guidance 190, 192 and 227) could be used. The ERG explained that an advantage of the Nafees model is that it explicitly incorporates the disutility of the main adverse effects associated with treatment. The ERG commented on the related issue of costing the treatment of adverse events, noting that the source of most resource use data was taken from an earlier trial of pemetrexed rather than PARAMOUNT. The ERG clarified that it would favour using the PARAMOUNT resource use data.

3.26 Regarding the use of the gamma distribution in the revised base case, the ERG re-iterated its position that the central difference in approach to modelling overall survival is that the manufacturer believed that a post-progression benefit of pemetrexed over placebo was plausible, whereas the ERG, on the basis of data from PARAMOUNT, did not. Accordingly, the ERG re-stated its belief that a common exponential distribution that removes the possibility of any difference in post-progression survival between the

treatments is a more appropriate parametric distribution for the purposes of projecting overall survival.

3.27 The ERG provided a revised exploratory analysis using the manufacturer's revised base case but using an exponential distribution to project survival, and amending the point at which projection starts to 37.2%, and using PARAMOUNT resource use data. When the Nafees utility values were also used in this analysis, the ICER was £93,361 per QALY gained (incremental costs of £14,782 and incremental QALYs of 0.1583). When the utility values from the unadjusted utility model were used, the ICER was £82,183 per QALY gained (incremental costs of £14,466 for a gain of 0.1760 QALYs).

3.28 Full details of all the evidence are in the manufacturer's submissions and the ERG reports, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pemetrexed, having considered evidence on the nature of non-squamous NSCLC and the value placed on the benefits of pemetrexed maintenance treatment following pemetrexed and cisplatin induction therapy by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee was aware of comments received from a patient group describing the limited life expectancy of people with NSCLC and of the importance to patients and their families of the availability of additional active therapy options. The Committee was also made aware of the most common symptoms experienced by

people with NSCLC including breathlessness, persistent cough, weight loss, listlessness and fatigue.

4.3 The Committee noted the evidence presented by the manufacturer on the use of pemetrexed maintenance treatment for people with advanced metastatic (stage IIIB and IV) non-squamous NSCLC, with performance status of 0–1, whose disease completely or partially responded or was stable after first-line treatment with pemetrexed plus cisplatin. The Committee was aware that this appraisal was concerned with the extension to the marketing authorisation for pemetrexed maintenance treatment after induction therapy with pemetrexed and cisplatin, and that NICE has already issued guidance on the use of pemetrexed following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (Pemetrexed for the maintenance treatment of non-small-cell lung cancer [NICE technology appraisal guidance 190]).

4.4 The Committee considered the decision problem as outlined in the final NICE scope for the appraisal, noting that within the scope, best supportive care (including bisphosphonates and palliative radiotherapy) was identified as the comparator. The Committee heard from the clinical specialists that standard practice for patients treated with pemetrexed-containing chemotherapy is observation and further treatment to be considered only at the time of disease relapse. The Committee therefore concluded that best supportive care was an appropriate comparator for this appraisal because it equated to the current practice of observation after first-line induction chemotherapy.

4.5 The Committee discussed the issue of performance status in relation to both first-line chemotherapy for advanced non-squamous NSCLC and maintenance treatment. It noted that NICE clinical guideline 121 (Lung cancer) recommends that

chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (World Health Organization [WHO] 0, 1 or a Karnofsky score of 80–100); chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug, the latter being either carboplatin or cisplatin; and that patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. The Committee heard from clinical specialists that in clinical practice most patients potentially eligible for chemotherapy for advanced NSCLC were of performance status 0 or 1 rather than performance status 2. However, whereas most patients with advanced non-squamous NSCLC with a performance status of 0 or 1 received palliative chemotherapy, a significantly smaller proportion of patients with a performance status of 2 were treated with chemotherapy. The clinical specialists indicated that whereas the combination of cisplatin and pemetrexed would only be used in patients with a performance status of 0 or 1, carboplatin-based chemotherapy was also used in this group too, as well as in patients with a performance status of 2. The clinical specialists also pointed out that maintenance pemetrexed would be considered for use in any patients of performance status 0 or 1 at the end of first-line chemotherapy whatever their performance status at the start of first-line chemotherapy. The Committee heard from the manufacturer that although the summary of product characteristics does not specify a patient's performance status in the wording of the maintenance indication (see section 4.1 of the summary of product characteristics), it does make reference to patients in the maintenance trials as having a performance status of 0 or 1 in section 5.1. The manufacturer therefore considered that treating patients with a performance status other than 0 or 1 would be

outside of the licensed indication for maintenance pemetrexed. The Committee concluded that although the licensed indication does not specify performance status for maintenance pemetrexed, it would not be usual clinical practice for a patient with a performance status other than 0 or 1 to receive pemetrexed maintenance treatment following induction therapy with pemetrexed plus cisplatin.

Clinical effectiveness

4.6 The Committee was aware that the only evidence of clinical effectiveness came from 1 randomised clinical trial (PARAMOUNT). It considered that PARAMOUNT was well designed. The Committee then discussed the applicability of the PARAMOUNT data to the population of people with NSCLC in England and Wales. It heard from the clinical specialists that patients in clinical trials are generally younger and fitter than those seen in clinical practice in England and Wales. The Committee noted that 32% of patients who entered PARAMOUNT had a performance status of 0 at the end of 4 cycles of induction chemotherapy. The Committee concluded that patients in PARAMOUNT were generally younger and fitter than those seen in clinical practice in England and Wales.

4.7 The Committee discussed the number of pemetrexed maintenance cycles that a patient would be likely to receive, conscious of the ERG's comment that the mean number of cycles of treatment with pemetrexed in PARAMOUNT was more than 7 cycles and that 6 cycles might be considered a likely maximum in UK clinical practice. However, the Committee heard from clinical specialists that patients would be treated until disease progression or unacceptable toxicity, or patient or physician choice to stop treatment early, rather than with a set number of cycles. On the

basis of the evidence put forward by the clinical specialists, the Committee concluded that patients would receive pemetrexed maintenance treatment until disease progression or unacceptable toxicity.

4.8 The Committee discussed and reviewed the progression-free survival and overall survival data from PARAMOUNT (see sections 3.3 and 3.4). The Committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.

4.9 The Committee noted the greater rates of grade 3 and 4 adverse reactions associated with pemetrexed maintenance treatment than with placebo, specifically increased hospitalisations, fatigue and blood transfusions. Increased grade 1 and 2 adverse reactions were also noted by the Committee, in particular nausea and vomiting, but there was no statistically significant difference in health-related quality of life between the pemetrexed and placebo arms of PARAMOUNT. The Committee concluded that treatment with pemetrexed maintenance therapy in this setting was associated with clinically significant but acceptable adverse reactions.

Cost effectiveness

4.10 The Committee considered the assumptions around resource use in the economic model submitted by the manufacturer. It first discussed the monitoring requirements for pemetrexed maintenance treatment. The Committee was aware that patients in

PARAMOUNT received a CT scan every 6 weeks, and heard from clinical specialists that a CT scan would be repeated every 2 to 3 months during maintenance treatment in UK clinical practice. The Committee noted that the manufacturer's original assumption was that 3% of patients would need additional scans, occurring every 24 weeks. The Committee noted that the revised base case increased the proportion of patients needing additional scans to 100% and increased the frequency of CT scans to once every 12 weeks. On the basis of the clinical specialists' comments, the Committee concluded that this was an acceptable assumption.

4.11 The Committee discussed the costs of post-progression chemotherapy in the manufacturer's base-case analysis. It was aware that the manufacturer's original base case had assumed that patients on pemetrexed would be 12% less likely to receive additional chemotherapy following progression than patients on placebo. It noted that the trial data did not support this assumption, because a similar proportion of patients in both groups received additional chemotherapy following progression. The Committee also considered that the time at which a patient's disease progresses on maintenance pemetrexed treatment would be later than for those who received placebo and that this might therefore have affected the timing and numbers of patients recorded in the trial as having post-progression chemotherapy. The Committee noted that the manufacturer had accepted this as an amendment and the revised base case assumed equal rates of post-progression chemotherapy between pemetrexed and placebo. The Committee concluded that this was an appropriate amendment.

4.12 The Committee welcomed the manufacturer's revised base-case (see section 3.22) but noted that some issues remained of continued concern: concomitant medication costs, utility model

design and survival projection. The Committee discussed the absence of the cost of the concomitant medications that are needed with pemetrexed (vitamin supplementation and dexamethasone) from the manufacturer's revised base case. The Committee heard from the manufacturer that a free 'supplementation pack' that includes vitamins and dexamethasone had been introduced to hospitals in the UK. The Committee was aware that the impact on the ICER of including the concomitant medication costs was small (around £100). The Committee concluded that the effect of including the concomitant medication costs on the ICER was not significant particularly when compared with the other outstanding issues and thus did not need to be considered further.

4.13 The Committee considered the method used for estimating utility employed within the economic model. It heard from the manufacturer that their preferred method of estimating utility was the 'unadjusted' mixed model based on the PARAMOUNT EQ-5D individual patient data because it gave intuitive utility values. The Committee agreed that the values were intuitive but remained concerned that the inclusion of a 'cycle' variable to account for changes in utility with treatment cycles in the adjusted model would cause significant instability (see section 3.25). The Committee discussed the alternative utility values from the Nafees model, and was aware that these were based on NSCLC patients receiving second-line treatment, rather than maintenance treatment. In addition, the Committee had reservations about using the Nafees utility model values (which are not aligned with EQ-5D methods) in preference to EQ-5D data from PARAMOUNT. The Committee welcomed the availability of EQ-5D data from the trial and agreed that these data should be used to provide the utility values for the model. However the Committee remained cautious about how the

unadjusted regression model had been specified to explore the effect of treatment on utility. Furthermore, the Committee was aware that, to accommodate the impact of a loss in utility (disutility) from an adverse effect of treatment, the manufacturer had calculated an average disutility for all pre- and post-progression health states, and applied these to the pre-progression health states only. Although the Committee accepted that disutility from treatment-related adverse events would only occur during the pre-progression phase (while a patient is still on treatment), it was not appropriate that the disutility value should be estimated from an average of the on-treatment and off-treatment times. The Committee concluded that although the unadjusted model had not been optimally executed and disutility had not been correctly estimated, the values were still preferable to those from the Nafees model, which were neither EQ-5D based, nor from the population of interest.

4.14 The Committee discussed the source of resource use data within the economic model. It heard from the ERG that the source of resource use data within the economic model was selected average costs taken from a previous trial in a different patient population (JMEN, a clinical trial for pemetrexed maintenance following non-pemetrexed-containing induction therapy) rather than PARAMOUNT. The Committee concluded that it was more appropriate to use PARAMOUNT costs because these were available for the population of interest.

4.15 The Committee considered the approaches to survival modelling. The Committee was aware that the key difference between the manufacturer's preferred approach and the ERG's exploratory analysis was whether or not patients treated with pemetrexed receive additional survival gains after their disease has progressed

and pemetrexed treatment has been discontinued. This was because the manufacturer's preferred parametric function for projecting survival (the gamma function) resulted in a significant post-progression benefit for pemetrexed, whereas the ERG's exponential function did not assume any difference between pemetrexed and placebo beyond the treatment phase. The Committee noted the ERG's Kaplan-Meier analysis of post-progression survival indicated that for the 2 trial arms, survival corresponded very closely. The Committee also understood from comments made by the clinical specialists at the first Committee meeting that a continued benefit of pemetrexed over best supportive care after disease progression is difficult to explain. The Committee heard from the manufacturer that it was not considered plausible that a patient would receive a benefit from pemetrexed throughout treatment and that the benefit would suddenly stop immediately on discontinuation of treatment. However the Committee noted that although it may not be plausible to assume an immediate end to the benefit of treatment on disease progression, this was not the same as assuming a significant benefit of pemetrexed over and above that of placebo, which was the effect of using the gamma distribution. During consultation the manufacturer highlighted Stein et al. 2009 and Stein et al. 2011 as evidence of treatment effect reducing tumour growth rates after treatment is stopped (using non-pemetrexed treatments) in patients with advanced prostate and renal cancer. The Committee considered that the findings in these papers did not support an extended benefit of chemotherapy following disease progression, because the only scenario in which post-treatment benefit was postulated occurred with a vaccine treatment. The Committee did not find any reason for basing its decision on anything other than the PARAMOUNT data, which did not show any evidence of a post-

progression benefit for pemetrexed over placebo. Accordingly, the Committee concluded that the ERG's approach to survival modelling using a long-term exponential distribution was more appropriate than the manufacturer's use of a gamma distribution.

4.16 The Committee considered the points on the survival curve from which the manufacturer and the ERG's analyses had projected survival estimates. The Committee noted that the manufacturer's revised base case adopted the ERG's approach in which a common level of survival was used as the start point of projection. It considered this to be an appropriate approach. However, the Committee noted that the revised base case used a common level of survival of 25% rather than the 20% point previously used by the ERG and accepted by the Committee. The Committee discussed the ERG's additional work in which a point of 37.2% was suggested (see section 3.24). The Committee heard from the ERG that it had chosen this level to equalise the projective portion in both arms, and because the Kaplan-Meier estimate and overall survival projective model estimate corresponded closely, minimising a potential source of bias. The Committee was aware that the choice of cut point is a matter of judgement and as such, any estimates come with some degree of uncertainty. Acknowledging this uncertainty, the Committee accepted the ERG's basis for the choice of 37.2% as the point from which to begin survival projection.

4.17 On the basis of its discussions (see sections 4.12 to 4.16), the Committee considered that the most appropriate ICER should be calculated using the revised assumptions around cost and resource use, the unadjusted utility model and the ERG's approach to survival modelling using the point at which survival in both arms was 37.2% as the point at which to start projection. The result of

combining these assumptions was confirmed by the ERG to produce an ICER of approximately £82,000 per QALY gained.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- Treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.19 Noting evidence from the National Lung Cancer Audit (2012) and the survival time of patients on placebo and best supportive care in PARAMOUNT, the Committee concluded that the life expectancy of patients with advanced non-squamous NSCLC is normally less than 24 months. The Committee also concluded that there was sufficient evidence to indicate that the treatment offers extension to life of at least 3 months, noting that both the manufacturer's and ERG's estimated mean overall survival gain was more than 3 months (4.2 months and 3.4 months respectively).

4.20 The Committee considered and discussed the patient population for which pemetrexed is licensed, taking into account all the therapeutic indications for pemetrexed identified in the summary of product characteristics. The Committee noted that pemetrexed has a UK marketing authorisation for the following indications:

- in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology
- as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy
- as monotherapy for the second-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology
- in combination with cisplatin for the treatment of chemotherapy-naive patients with unresectable malignant pleural mesothelioma.

4.21 The Committee discussed the small patient population criterion. It heard from NICE that, for treatments for small groups of patients, higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product if the licensed indications only apply to a small potentially eligible patient population. It further heard that the case for reduced cost effectiveness weakens as the potential total population for a product increases. Therefore taking into account the cumulative population covered by all the indications in the marketing authorisation needs to be considered. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under

these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. The Committee considered that the calculation of the total population should reflect only the population covered by the licensed indications in the countries where NICE guidance had formal effect (that is, England and Wales). The Committee recognised that in the case of patients having first-line chemotherapy with pemetrexed in combination with cisplatin and then continuing on maintenance pemetrexed, this represented additional opportunities for the manufacturer to recoup the costs of development for pemetrexed.

4.22 The Committee considered the population size for the indication for pemetrexed as first-line therapy. It was aware that the licensed indication is that pemetrexed should be given in combination with cisplatin, and, on the basis of comments from the clinical specialists, that only patients with a performance status of 0–1 would be considered for treatment with cisplatin. However, for patients who are fit enough to tolerate this combination, the Committee heard from the clinical specialists that this would be the first-line treatment of choice. The Committee noted that, according to the National Lung Cancer Audit (2012), the number of patients with confirmed NSCLC who are of performance status 0–1 and who have stage IIIB or IV disease is 6698. It understood that 68% of these patients would have non-squamous histology (NICE clinical guideline 121), therefore the potential population eligible for first-line therapy with pemetrexed would be 4555.

4.23 The Committee considered the population size for the maintenance indication for pemetrexed. It was aware that the licence extension meant that pemetrexed would be an option for patients as

'continuation maintenance' (that is, pemetrexed maintenance treatment following induction therapy with pemetrexed in combination with cisplatin) or 'switch maintenance' (that is, pemetrexed maintenance treatment following induction therapy which does not include pemetrexed). The Committee noted comments received during consultation from the manufacturer that, of those eligible for first-line treatment (4555), 55.2% (2514) receive first-line chemotherapy and of these 40% (1006) receive pemetrexed plus cisplatin. Of these, the manufacturer estimated that 58.4% (588) would be eligible for pemetrexed continuation maintenance treatment. The Committee accepted this number. Regarding switch maintenance, the Committee noted that, if 1006 people receive a pemetrexed-containing first-line induction therapy, the remainder of the total population (that is, 2514 minus 1006, or around 1500) would be eligible for switch maintenance treatment. The Committee was aware that around 74% (JMDB study report) of patients would respond to induction therapy and therefore be eligible for maintenance treatment. This would suggest around 1110 people would be eligible for switch maintenance treatment. The Committee concluded that the total population for both continuation and switch maintenance treatment would be approximately 1500.

4.24 The Committee considered the population size for the second-line treatment of NSCLC for pemetrexed. It noted that anyone who did not receive pemetrexed as induction or maintenance therapy (that is, those patients of performance status 2) would be potentially eligible for second-line therapy with pemetrexed following disease progression. It noted the manufacturer's estimate that 462 people receive first-line chemotherapy that does not include pemetrexed. The Committee accepted this estimate for the population of people

potentially eligible to receive pemetrexed as a second-line treatment.

4.25 The Committee was aware that pemetrexed also has a marketing authorisation for mesothelioma. The Committee noted that, according to the National Lung Cancer Audit (2012), the number of patients with mesothelioma is 1825. It is understood that 88% of these patients would have advanced disease; therefore the potential population eligible for pemetrexed would be 1606 with mesothelioma.

4.26 The Committee considered the total population size for which pemetrexed has a licence. It noted that its calculations did not include those people who present at an earlier stage of disease, but who relapse after surgery or radiotherapy, and then go on to receive pemetrexed-based chemotherapy. The Committee concluded that the total patient population would be more than 8000, which it did not consider to represent a small population. The Committee concluded that pemetrexed did not meet the small total patient population criterion. The Committee therefore concluded overall that pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin could not be considered under the supplementary advice to the Committee on end-of-life treatments.

4.27 The Committee noted that even if the end-of-life considerations were taken into account, the most plausible ICER for pemetrexed maintenance following induction therapy with pemetrexed and cisplatin compared with placebo plus best supportive care was substantially higher than would normally considered to be a cost effective use of NHS resources. Therefore the Committee concluded that pemetrexed maintenance treatment should not be recommended for treating locally advanced or metastatic NSCLC

other than predominantly squamous cell histology in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.

4.28 The Committee discussed whether its preliminary recommendations for pemetrexed as a maintenance therapy following induction with pemetrexed plus cisplatin were associated with any issues related to the equality legislation and the requirement for fairness. The Committee was aware that NICE technology appraisal guidance 190 (TA190) recommends pemetrexed as an option for the maintenance treatment of people with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel. The Committee discussed whether its preliminary recommendations could be considered unfair given the recommendations in TA190, and that the difference between the populations in TA190 and the current appraisal was in terms of the first-line treatment received. The Committee agreed that first-line treatment is not linked to the protected characteristics covered in the equality legislation. The Committee was aware that it needs to make a decision for each appraisal based on the evidence before it and this is what it has done in this case. The Committee agreed that its decision on pemetrexed as a maintenance therapy following induction with pemetrexed plus cisplatin was made because pemetrexed maintenance was not cost effective in this population. Furthermore, even if there was any unfairness, given the high ICER of approximately £82,000 per QALY gained, the Committee agreed that the recommendation could be justified and was in line with the Committee's role and the application of the cost-effectiveness criteria, and was a proportionate means of achieving a legitimate

aim. The Committee had not identified any special factors which would require or justify making a positive recommendation despite the very high ICER.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer	Section
Key conclusion		
Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology for people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.		1.1
The Committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.		4.8
The Committee considered that the most plausible ICER was approximately £82,000 per QALY gained. Therefore the Committee concluded that pemetrexed maintenance treatment should not be recommended for treating locally advanced or metastatic NSCLC other than predominantly squamous cell histology in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.		4.17, 4.27
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from a patient group of the importance to patients and their families of the availability of additional active therapy options.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.	4.8
What is the position of the treatment in the pathway of care for the condition?	Pemetrexed has a marketing authorisation as 'monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy'.	2.1

Adverse reactions	The Committee concluded that treatment with pemetrexed maintenance therapy in this setting was associated with clinically significant but acceptable adverse reactions.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence of clinical effectiveness was derived from the PARAMOUNT trial. This was an international, multicentre (83 sites across 16 countries including the UK), double-blind, phase III, randomised trial in patients with stage IIIB or stage IV non-squamous NSCLC whose disease had not progressed after 4 cycles of pemetrexed plus cisplatin induction therapy. The Committee considered that PARAMOUNT was well designed.	3.1 4.6
Relevance to general clinical practice in the NHS	The Committee concluded that the patients in the PARAMOUNT trial were generally fitter and younger than those seen in clinical practice in England and Wales.	4.6
Uncertainties generated by the evidence	The Committee concluded that patients in PARAMOUNT were generally younger and fitter than those seen in clinical practice in England and Wales.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups were identified during the appraisal.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Noting the clinical trial results (PARAMOUNT) the Committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in median progression-free survival of 1.68 months and median overall survival of 2.85 months.	3.3–3.4, 4.8

Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer submitted a state-transition Markov model to evaluate the cost effectiveness of pemetrexed compared with placebo.	3.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was not persuaded by the manufacturer's approach to the modelling of progression-free survival and overall survival. The Committee also concluded that more accurate estimates of resource use and utility parameters were available than those used in the manufacturer's revised base case.	4.15-4.17 4.12–4.14
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Patients in PARAMOUNT were asked to rate their present health condition using the EQ-5D instrument. The manufacturer noted that the trial data did not provide values suitable for the pre- and post-progression health states, therefore a mixed regression analysis was carried out. No significant and substantial health-related benefits that have not been captured by the QALY calculation were identified either in the submission or at the Committee meeting.	3.11
Are there specific groups of people for whom the technology is particularly cost effective?	No clinically relevant subgroups were identified during the appraisal.	
What are the key drivers of cost effectiveness?	The different approaches to estimating overall survival for the lifetime of the model between the manufacturer's revised base case and ERG's analyses resulted in a difference of around £25,000 per QALY gained.	3.22, 3.27, 4.17
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that the most plausible ICER was approximately £82,000 per QALY gained.	4.17

Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	
End-of-life considerations	The Committee considered that the total population for whom pemetrexed is licensed was not small enough for the end-of-life advice to apply. It noted that even if the supplementary advice on end-of-life treatments was taken into account, the most plausible ICER was higher than that normally considered to be cost effective.	4.18 to 4.27
Equalities considerations and social value judgements	The Committee did not identify any special factors which would require or justify making a positive recommendation despite the very high ICER.	4.28

5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation. Further information is available on the NICE website.

Published

- Lung cancer: The diagnosis and treatment of lung cancer. NICE clinical guideline 121 (2011).
- Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 227 (2011).
- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 (2010).
- Pemetrexed for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 190 (2010).
- Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE technology appraisal guidance 181 (2009).
- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008).
- Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). NICE technology appraisal 148 (2008).

There is a NICE pathway on lung cancer.

Under development

- Erlotinib and gefitinib for the treatment of non-small-cell lung cancer following prior chemotherapy (review of TA162 and TA175). NICE technology appraisal guidance (publication expected June 2014).
- Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. NICE diagnostics guidance (publication expected September 2013).

- Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. NICE technology appraisal guidance (publication expected September 2013).

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive at the same time as NICE technology appraisal guidance 190 and 181, or earlier if the patent for this technology expires before that time. The review decision for these technology appraisals will take place within 6 months of the publication of an independent Health Technology Assessment report on 'First-line therapy for adult patients with non-small-cell lung cancer' that is currently being compiled by the Liverpool Review and Implementation Group (LRiG), Liverpool University. This paper was published in July 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark
Chair, Appraisal Committee
August, 2013

8 Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Aomesh Bhatt
Director of Regulatory and Medical Affairs, Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Tracey Cole
Lay Member

Dr Ian Davidson
Senior Lecturer in Physiotherapy, Manchester Metropolitan University

John Dervan
Lay Member

Professor Simon Dixon
Professor of Health Economics, University of Sheffield

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Christopher Earl
Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Dr Paul Hepple
General Practitioner, Muirhouse Medical Group

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Dr Steven Julious
Reader in Medical Statistics, University of Sheffield

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Warren Linley
Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie
Lay Member

Dr Alison Talbot-Smith
Consultant in Public Health, Herefordshire Clinical Commissioning Group

Charles Waddicor
Chief Executive, NHS Berkshire West

Professor Carolyn Young
Consultant Neurologist, Walton Centre for Neurology and Neurosurgery

B NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mark Minchin

Technical Lead

Joanne Holden

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRIG):

- Greenhalgh J, Bagust A, Blundell M et al. Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer, December 2012

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. 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 and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Lilly UK

II Professional/specialist and patient/carer groups:

- Roy Castle Lung Cancer Foundation
- British Thoracic Society
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- British Thoracic Oncology Group
- Liverpool Reviews and Implementation Group (LRIG)
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

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

- Dr Jesme Fox nominated by Roy Castle Lung Cancer Foundation – patient expert *(written evidence only)*
- Dr Riyaz Shah nominated by Lilly UK – clinical specialist
- Dr Yvonne Summers nominated by the Royal College of Physicians – clinical specialist

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Lilly UK