NICE National Institute for Health and Care Excellence

NICE guidance

Pemetrexed for the maintenance treatment of non-small-cell lung cancer

Technology appraisal guidance
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1 Recommendations

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

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2 Information about pemetrexed

2.1 Pemetrexed disodium (Alimta, Eli Lilly and Company) is an antifolate agent that works by disrupting folate-dependent metabolic processes that are essential for cancer cell replication and survival. Pemetrexed has a marketing authorisation for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. The marketing authorisation states that first-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. (A platinum doublet is platinum-based chemotherapy plus one other drug).

2.2 The summary of product characteristics (SPC) states that the recommended dosage is 500 mg per m^2 body surface area, administered as a 10-minute intravenous infusion 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.

2.3 The SPC reports that the most common adverse effects include nausea, vomiting, fatigue, leukopenia (particularly of the neutrophil component), skin rash, mucositis and liver function abnormalities. For full details of side effects and contraindications, see the SPC.

2.4 The acquisition cost of pemetrexed is £800 for a 500-mg vial (excluding VAT, BNF 57th edition). The cost per patient, assuming an average of 8 cycles and a body surface area of 1.79 m^2, is approximately £12,076. Costs may vary in different settings because of negotiated procurement discounts.

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3 Committee discussion

The manufacturer's submission

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

3.1 The manufacturer's submission contained evidence on the clinical effectiveness of pemetrexed maintenance therapy compared with best supportive care. The manufacturer stated that pemetrexed is the only chemotherapy currently licensed for the maintenance treatment of non-small-cell lung cancer in the UK and worldwide. Therefore, the comparator used in the clinical trial was placebo plus best supportive care.

3.2 The manufacturer identified one phase 3 multicentre, double-blind randomised control study (the JMEN trial) which evaluated the efficacy of maintenance treatment with pemetrexed monotherapy in people with advanced or metastatic (stage IIIB and IV) non-small-cell lung cancer whose disease had not progressed following treatment with platinum-based first-line chemotherapy. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial randomised 663 patients with squamous and non-squamous non-small-cell lung cancer to pemetrexed plus best supportive care (n=441) or placebo plus best supportive care (n=222). Patients in both arms of the trial received concomitant medication with folic acid, vitamin B12 and dexamethasone. Patients in the pemetrexed arm received pemetrexed 500 mg per m^2 on day 1 of each 21-day cycle, administered as a 10-minute infusion, plus best supportive care, until disease progression. Patients in the placebo arm received normal saline (0.9% sodium chloride) on day 1 of each 21-day cycle, administered as a 10-minute infusion, plus best supportive care, until disease progression. The manufacturer presented evidence for the subgroup of non-squamous non-small-cell lung cancer (n=481) in accordance with the licensed indication. Of this subgroup, 325 patients received pemetrexed plus best supportive care and 156 received placebo plus best supportive care.

3.3 The mean number of pemetrexed cycles for the non-squamous population was

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8.0 (standard deviation 8.62) and the median was 6.0 cycles (25th to 75th percentile 2.5 to 10.0). There were a few patients who received between 20 and 55 cycles (7% to 11% of patients received more than 20 cycles).

3.4 The primary outcome of the JMEN trial was initially overall survival, but this was changed to progression-free survival during the trial. Median progression-free survival was significantly longer with pemetrexed plus best supportive care compared with placebo plus best supportive care (4.5 months versus 2.6 months, hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.36 to 0.55, p<0.00001). A subgroup analysis for patients with adenocarcinoma (a type of non-squamous non-small-cell lung cancer) reported similar improvement in progression-free survival with pemetrexed plus best supportive care compared with placebo plus best supportive care (4.7 months versus 2.6 months, HR 0.45, 95% CI 0.35 to 0.59, p<0.00001). Secondary outcomes of the JMEN trial included tumour response, disease control rate and time to worsening of symptoms. The JMEN trial demonstrated a statistically significant median overall survival benefit of 5.2 months for the non-squamous population in favour of pemetrexed compared with placebo (15.5 months versus 10.3 months, HR 0.70, 95% CI 0.56 to 0.88, p=0.002). Similar results were reported for the adenocarcinoma subgroup. For the non-squamous population, 1-year overall survival in the pemetrexed plus best supportive care arm was 60% compared with 42% in the placebo arm. The difference in overall survival was smaller at 2 years (28% for pemetrexed compared with 22% for placebo). The trial reported similar results for the 1- and 2-year overall survival in the adenocarcinoma subgroup. Statistically significant improvements in tumour response, disease control rate and time to worsening of symptoms were reported for pemetrexed plus best supportive care compared with placebo plus best supportive care. The manufacturer's submission noted the absence of trial-based health-related quality-of-life data because many of the patients did not complete quality-of-life surveys.

3.5 The manufacturer's submission reported higher rates of grade 3 and 4 adverse events with pemetrexed plus best supportive care than with placebo plus best supportive care (6.3% versus 2.3%). Fatigue and neutropenia were the most commonly reported adverse events. There were significantly higher percentages of patients in the pemetrexed arm who discontinued treatment, required transfusion, erythropoiesis-stimulating agents or hospitalisation because of drug-related toxicity, or withdrew from the study.

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3.6 The manufacturer developed a trial-based model which included three health states (not progressed, progressed and terminal state). Patients entered the model at the start of maintenance treatment, which was assumed to begin after four cycles of first-line chemotherapy (consisting of a platinum doublet with gemcitabine, paclitaxel or docetaxel) in patients who had no evidence of disease progression. Patients in the placebo arm received 'watch and wait' treatment and best supportive care, and patients in the pemetrexed arm received treatment plus best supportive care in 21-day cycles until disease progression. After disease progression patients were eligible for second-line treatment.

3.7 The economic model had a time horizon of 72 months (29-month overall survival data from the JMEN trial extrapolated to 72 months using an exponential survival function). Treatment effects that were included in the model were overall survival, adverse events and health-related quality of life. All effectiveness data used in the model, apart from health-related quality of life, were trial based. Trial data on progression-free survival were not used in the economic model. The number of treatment cycles in the trial was used as a proxy for the time to progression in the pemetrexed arm. The disutility of adverse events was not included in the base-case model but was captured in the sensitivity analyses.

3.8 In the JMEN trial, patients received pemetrexed treatment until their disease progressed. Although this resulted in patients receiving up to 55 cycles (with a mean of 8 cycles), the manufacturer's submission noted that clinical specialists suggested that if maintenance treatment were introduced to UK clinical practice, patients would receive a maximum of 10 cycles of pemetrexed maintenance treatment. The manufacturer therefore incorporated a 'capping rule' in which the maximum number of cycles of pemetrexed was set at 1 standard deviation above the mean, equivalent to a maximum of 17 cycles (with a new mean of 5.84) for the non-squamous population, and a maximum of 18 cycles (with a new mean of 6.16) for the adenocarcinoma population. The new means were used in the manufacturer's base case.

3.9 In the absence of data on health-related quality of life from the JMEN trial, utility data were taken from literature estimates. The manufacturer mainly used a study on the second-line treatment of non-small-cell lung cancer by Nafees et al. (2008). It involved 100 members of the public interviewed with visual analogue scale and standard gamble techniques to generate societal values on utilities in

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lung cancer. In addition, the manufacturer also used data from a study by Berthelot et al. (2000). Based on these two studies, the manufacturer assigned a utility of 0.66 to patients on pemetrexed and 0.58 to patients on placebo.

3.10 The manufacturer's base-case analysis compared pemetrexed plus best supportive care with placebo plus best supportive care in the non-squamous population. The incremental cost-effectiveness ratio (ICER) for pemetrexed compared with best supportive care in the non-squamous population was calculated to be £33,732 per QALY gained, based on an incremental cost of £9,137 and an incremental QALY of 0.27. The ICER for the adenocarcinoma subgroup was £39,364 per QALY gained, based on an incremental cost of £9,554 and an incremental QALY of 0.24.

3.11 The manufacturer also presented the ICERs for 36 one-way sensitivity analyses and a number of scenarios that explored the effect of per-vial costing and cycle capping, and included a best-case and worst-case scenario. Most of the results in the one-way sensitivity analyses had little effect on the base-case ICERs. However, two results did have a large effect:

- When the incremental survival of pemetrexed was reduced from 5.3 months in the base case to 1.15 months, the ICER increased to £105,826 per QALY gained.
- When the overall survival advantage was reduced by 9.5%, to allow for the patients excluded with the base-case capping rule, the ICER increased to £48,290 per QALY gained.

3.12 The ERG reviewed the evidence submitted for clinical and cost effectiveness, focussing on the non-squamous population in accordance with the licensed indication. The ERG stated that the JMEN trial was reasonably well designed, incorporating blinding, placebo control and independent monitoring of investigator assessments. The clinical outcomes reported from the trial addressed the outcomes that were relevant to the appraisal (overall survival, progression-free survival, tumour response, adverse events and health-related quality of life).

3.13 The ERG raised concern about the conduct of the trial, its generalisability to the UK patient population and the uncertainty around the estimates of cost

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effectiveness. The ERG noted that the inclusion criteria of the JMEN trial were restricted to younger patients with a good performance status (ECOG 0 or 1) and with few comorbidities. Only a relatively small proportion of the total number of non-small-cell lung cancer patients treated in clinical practice in the UK has an ECOG performance status of 0 or 1.

3.14 The ERG did not consider that adequate justification was given for changing the primary endpoint of the JMEN trial from overall survival to progression-free survival. It considered that this decision had the effect of truncating the data available for analysis of overall survival, which was of critical importance to the economic evaluation. The ERG also considered the high rate of missing data on health-related quality of life to be a limitation. It was not clear how patients' quality of life would be affected by maintenance treatment with pemetrexed.

3.15 The ERG noted that 53% of patients in the pemetrexed arm and 36% of patients in the placebo arm of the JMEN trial received second-line treatments that are not used in UK clinical practice. This may have influenced the overall survival estimates observed in the trial and may mean that the results of the trial do not reflect the survival benefits that might be expected in UK clinical practice.

3.16 The ERG was concerned that the key clinical evidence was derived from a histological subgroup of the trial population, but that histology was not included in the stratification for the randomisation procedure.

3.17 The ERG assessed the manufacturer's cost-effectiveness analysis. It commented on the version of the model which used the exponential (rather than Weibull) projection as the basis for comparison (this being the manufacturer's base case). The ERG noted that the capping of pemetrexed treatment at 17 cycles was much less than the maximum of 55 cycles in the JMEN trial. The ERG considered that this limited the costs of maintenance treatment with no similar limitation on the benefits accrued from the use of pemetrexed, which led to bias in favour of pemetrexed. The ERG considered that the most appropriate base case should have included the full costs and benefits of maintenance treatment based on the number of cycles received in the JMEN trial. The ERG conducted an analysis in which the number of treatment cycles was not capped. This increased the ICER from £33,732 per QALY gained to £43,179 per QALY gained.

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3.18 The ERG considered that the discounting applied in the model was based on inappropriate assumptions. All maintenance chemotherapy cycles were assumed to occur in the first year (consistent with the imposed maximum cycles limit but not with the trial data), all second-line chemotherapy took place in the first year, all best supportive care was assumed to occur only in years 1 or 2 and all terminal care was assigned to year 3.

3.19 The ERG did not consider the additional monitoring of patients on pemetrexed chemotherapy (who were assessed every two cycles) to be consistent with UK clinical practice. It considered the appropriate follow up to be at 3, 6 and 12 months and every 6 months thereafter until progression for the best supportive care arm, and every four cycles (12 weeks) until progression in the pemetrexed arm. The ERG also noted that the body surface area distribution used in the model was not representative of the UK population because 35% of the trial population was Asian (from China, Korea, Taiwan and India).

3.20 The ERG noted that no direct use was made in the model of the primary trial outcome (progression-free survival) and the duration of maintenance therapy was used as a proxy. The ERG also expressed concerns that in the model the overall survival of patients who received second-line treatment was assumed to be the same as those who did not.

3.21 The ERG did not consider it appropriate for patients entering the model at randomisation who were in the same health state (without disease progression) to be assigned different utility values (0.66 for patents in the pemetrexed arm and 0.58 for patients in the placebo arm). This was not consistent with data from the JMEN trial in which the rate of grade 3 or 4 fatigue was noticeably higher in the pemetrexed arm (3.66%) than in the placebo arm (0.64%). When the ERG used utility values which incorporated the disutility associated with adverse events (0.6568 in the pemetrexed arm and 0.6628 in the placebo arm) the ICER increased from the base case of £33,732 per QALY gained to £36,798 per QALY gained.

3.22 The ERG considered that the manufacturer did not adequately justify the choice of parameters and parameter values used in the one-way sensitivity analyses. The ERG also expressed concern that a probabilistic sensitivity analysis had not been undertaken. When the ERG conducted an approximate probabilistic

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sensitivity analysis based on the overall survival gain and the mean number of treatment cycles from the individual patient data the cost-effectiveness acceptability curve showed that pemetrexed maintenance treatment would have zero probability of being cost effective at a threshold of £30,000 per QALY gained and 50% probability of being cost effective at a threshold of approximately £51,000 per QALY gained.

3.23 The ERG identified other concerns with the cost-effectiveness analysis, including:

3.24 The half-cycle correction applied to survival estimates appeared to be inappropriate. The ERG considered that the correct approach would be to use the area under the curve from the trial analysis unaltered, and then calculate 'mid-cycle' corrected estimates for the remainder of the model duration derived from a parametric model.

3.25 Post progression costs and survival values had been double discounted.

3.26 A minor error in the calculation of the proportion of patients assumed to receive docetaxel or erlotinib as second-line treatment. When this was corrected, the manufacturer's base-case ICER increased slightly.

3.27 The ERG investigated the impact of unlimited cycles of treatment, revised utility values, revised discounting assumptions, and increased cost of monitoring based on a model populated with individual patient data. The cumulative effect of these changes was an increase in the ICER for pemetrexed maintenance treatment from the manufacturer's estimated base case of £33,732 per QALY gained to £51,192 per QALY gained. The number of treatment cycles and utility revision had the most impact on the ICER.

3.28 The manufacturer presented a revised cost-effectiveness analysis to address the concerns raised by the Committee. The revised analysis included a probabilistic sensitivity analysis with an exponential extrapolation survival function and presented six scenarios in which the duration of treatment and the utility values in the pemetrexed and placebo arms were varied (Three different treatment durations were presented, each with two possible utility assumptions, giving a total of six scenarios). The different treatment durations considered were: 1 year (a maximum of 17 cycles), 2 years (a maximum of 35 cycles) and treatment until

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disease progression in accordance with the JMEN trial (a maximum of 55 cycles). The survival benefits modelled for each treatment duration were consistent with those seen in trial patients. Utility was either the same in both arms (0.66) or a lower utility was assigned to the pemetrexed arm (0.657) compared with the placebo arm (0.663). The ICERs for pemetrexed compared with best supportive care ranged from £46,137 per QALY gained to £50,286 per QALY gained, with a 46% to 58% probability of being cost effective at a threshold of £50,000 per QALY gained.

3.29 The ERG commented on the manufacturer's revised analysis and examined scenario 5 in detail. This scenario represented treatment until disease progression, used the entire trial population and incorporated a utility of 0.663 for the placebo arm and 0.657 for the pemetrexed arm. The ERG noted that most of the changes made by the manufacturer were those required to accommodate a probabilistic sensitivity analysis. The ERG also noted that the changes were implemented appropriately.

3.30 The ERG conducted a probabilistic sensitivity analysis on scenario 5 which incorporated all of the amendments suggested in their original analysis (see section 3.23). The ERG also presented the results of a probabilistic sensitivity analysis using an exponential and a Weibull extrapolation of the trial data. The ICER for pemetrexed compared with best supportive care using the exponential survival function was £56,903 per QALY gained using deterministic analysis and £47,168 per QALY gained using probabilistic analysis, with a 57.71% probability of being cost effective at a threshold of £50,000 per QALY gained. When the Weibull function was applied, the ICER for pemetrexed compared with best supportive care was £57,082 per QALY gained using deterministic analysis and £50,673 per QALY gained using probabilistic analysis, with a 49.70% probability of being cost effective at a threshold of £50,000 per QALY gained.

3.31 Full details of all the evidence are in the manufacturer's submission and the ERG report.

Consideration of the evidence

3.32 The Appraisal Committee reviewed the data available on the clinical and cost

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effectiveness of pemetrexed having considered evidence on the nature of non-small-cell lung cancer and the value placed on the benefits of pemetrexed by clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

3.33 The Committee considered current UK practice for the treatment of people with non-squamous non-small-cell lung cancer. The Committee heard from clinical specialists that patients undergo induction with a platinum doublet of carboplatin or cisplatin in combination with gemcitabine, paclitaxel, vinorelbine or docetaxel. The Committee was also aware of the recommendation in NICE's technology appraisal guidance on pemetrexed for the first-line treatment of non-small-cell lung cancer. After induction, patients are monitored but receive no chemotherapy until progression. Patients whose disease progresses only receive second-line chemotherapy if they have a good performance status. In the UK, this is normally docetaxel or erlotinib. Patients who do not receive second-line chemotherapy receive best supportive care, which can include palliative radiotherapy.

3.34 The Committee heard that maintenance treatment after first-line treatment is a new concept in lung cancer and is not currently practised in the UK. The Committee also heard from clinical specialists that pemetrexed has fewer adverse events associated with its use compared with many other chemotherapies offered for the treatment of non-small-cell lung cancer. The aim of maintenance treatment with pemetrexed is to prolong the period of remission after first-line chemotherapy and possibly increase eligibility for second-line chemotherapy.

3.35 The Committee noted that the clinical effectiveness evidence for pemetrexed for the maintenance therapy of non-small-cell lung cancer was based on the JMEN trial, and noted that the overall survival achieved with pemetrexed was higher than for people receiving best supportive care. The Committee considered the trial to be generally well designed but had a number of concerns over the interpretation of the trial results (see section 3.36 to 3.41).

3.36 The initial primary endpoint was changed from overall survival to progression-free survival during the course of the trial. The Committee heard from the

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manufacturer that this was done after consultation with regulatory authorities in the USA and the change was implemented before any trial data had been analysed.

3.37 The evidence in the manufacturer's submission was from the non-squamous histological subgroup of the trial but histology was not a factor in the randomisation process. However, the Committee heard from the clinical specialists that the histological groups were reasonably balanced between the two arms of the trial and that lack of histological testing as part of the randomisation would not have significantly affected the outcome of the analysis. The clinical specialists also told the Committee that although definitive histological testing is variable in practice, the trial strategy was a reasonable reflection of what would be done in non-trial conditions.

3.38 In the trial treatment cycles were only limited by disease progression. The Committee heard from clinical specialists that patients would continue to receive pemetrexed while they were responding to treatment and so the trial did reflect the likely UK clinical practice. Therefore, the Committee was concerned that the capping in the manufacturer's original economic model was not consistent with clinical practice (see section 3.44).

3.39 None of the trial centres were located in the UK and one third of the trial population was Asian (from China, Korea, Taiwan and India). The Committee heard from the clinical specialists that although this ethnic group has a relatively favourable prognosis for non-small-cell lung cancer, it would have the same relative benefit from treatment with pemetrexed as the UK population.

3.40 There was an imbalance in the use of second-line treatments in the trial, and the Committee was concerned about how this was used in the manufacturer's economic model (see section 3.46).

3.41 The Committee was concerned that insufficient health-related quality-of-life data had been collected from the trial to enable their inclusion in the economic modelling. The Committee heard from clinical specialists and the manufacturer that trial patients who are in progressive disease after first- and second-line treatment are less likely to complete quality-of-life surveys, making it hard to get health-related quality-of-life data.

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3.42 The Committee considered the population eligible for maintenance treatment. The Committee heard from clinical specialists that patients who receive first-line treatment usually have a good performance status, and that approximately one third of patients will progress while on first-line chemotherapy. The Committee also considered how patients are monitored in UK clinical practice. The Committee heard that although computer tomography (CT) scanning is not routinely used to monitor patients in UK clinical practice, it is likely that patients receiving pemetrexed maintenance treatment would undergo more CT scans to confirm that they have not progressed.

Cost effectiveness

3.43 The Committee considered the manufacturer's submitted cost-effectiveness analysis and the ERG's critique. The manufacturer's base case stated that the incremental cost of pemetrexed compared with best supportive care was £9,137 and the incremental QALY was 0.27, giving an ICER of pemetrexed compared to best supportive care of £33,732 per QALY gained. However, the Committee was aware of several concerns that the ERG had described in the calculation of this base case. These included: the modelling of overall survival, the capping of the number of treatment cycles but not the associated benefits, the different utilities assigned to patients in the same initial health state, the handling of second-line treatment effects and the absence of a probabilistic sensitivity analysis.

3.44 The Committee noted the 29-month overall survival data from the trial were extrapolated to 6 years in the model. It noted that the exponential curve applied in the base case did not fit the data well. The Committee noted that the manufacturer's analysis using a Weibull model was also plausible and that the ICERs were higher when Weibull models were used, suggesting that the figure in the base case might be at the lower end of the likely range. The Committee also expressed concern that the primary outcome in the trial (progression-free survival) was not captured in the model and number of cycles of treatment was used as a proxy.

3.45 The Committee considered the capping of costs in the manufacturer's original model at a maximum of 17 cycles. The Committee was informed by the manufacturer that clinical advice suggested that most benefit is derived in the

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first 8 to 10 cycles of treatment, which informed their decision to cap the cycles at 17 (1 standard deviation above the mean of 8 cycles). However, the Committee heard that in other cancers where patients receive maintenance treatment, cycles are not capped. The Committee considered that when capping was assumed, it had the effect of constraining the costs of maintenance therapy without a corresponding effect on the benefits accrued from use of pemetrexed, therefore building an essential bias in the economic evaluation in favour of pemetrexed.

3.46 The Committee considered the utility estimates assigned to patients in different arms of the model. It noted that in the manufacturer's original analysis, patients who entered the trial in the same health state were assigned higher utilities in the pemetrexed arm than in the placebo arm of the model – biasing the model in favour of pemetrexed. The Committee also noted that the disutilities of adverse events associated with pemetrexed were not modelled in the base case. Although the clinical specialists said that a minority of patients may feel better on pemetrexed maintenance treatment because their tumour shrank, the Committee was not persuaded that this justified the manufacturer's difference in utility between the two arms. The Committee considered the ERG's re-analysis of the model, which used a slightly lower utility for progression-free disease in the pemetrexed arm compared with the placebo arm, to be more appropriate. The Committee noted that this approach was adopted by the manufacturer in the revised analysis.

3.47 The Committee considered the six scenarios of the revised analysis presented by the manufacturer. The Committee also considered the ERG analysis of scenario 5, which corrected the utility estimates, removed cycle capping, performed an approximate probabilistic sensitivity analysis and also corrected discounting errors. The Committee considered scenario 5 to represent the most plausible assumptions for modelling the cost effectiveness of pemetrexed maintenance treatment compared with best supportive care. The Committee considered that the manufacturer's revised analysis had adequately addressed the main concerns identified in the original model. The Committee considered the updated ICERs presented for scenario 5 by the manufacturer (£47,000 per QALY gained) and the ERG (which ranged from £47,000 per QALY gained with the exponential model to £51,000 per QALY gained with the Weibull model) to be reliable.

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3.48 The Committee considered the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of patients with a short life expectancy and which 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:

- The 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 into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust.

3.49 The Committee discussed whether the benefit provided by pemetrexed for the maintenance treatment of non-small-cell lung cancer fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee understood that patients with stage IIIB or IV non-small-cell lung cancer who receive no treatment usually survive for about 7 to 10 months. The Committee considered the evidence from the pemetrexed randomised controlled trial (the JMEN trial) that showed a median survival benefit of 5.2 months for pemetrexed versus placebo. The Committee agreed that the data from the trial were sufficiently robust and that maintenance treatment with pemetrexed would increase overall survival by more than 3 months. The Committee considered that the estimated population for whom pemetrexed is licensed is currently small enough to allow the end-of-life advice to apply. The Committee concluded that the evidence submitted by the manufacturer was robust enough to show that maintenance treatment with pemetrexed fulfilled the criteria for the supplementary advice from NICE (see section 3.49).

3.50 The Committee considered the evidence presented by the manufacturer in the

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revised analysis to be robust. The Committee also considered the ERG's exploratory analysis, which demonstrated that the ICER for pemetrexed compared with best supportive care was about £47,000 per QALY gained. The Committee was persuaded that the most plausible ICER for pemetrexed compared with best supportive care was approximately £47,000 per QALY gained and, with reasonable certainty, was below £50,000 per QALY gained. The Committee considered this ICER, taking into account the end-of-life criteria. The Committee considered that the additional weight that would need to be assigned to the QALY benefits for the ICER to fall within the plausible range was acceptable. Therefore, the Committee recommended pemetrexed as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology, if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

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4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-small-cell lung cancer and the healthcare professional responsible for their care thinks that pemetrexed is the right treatment, it should be available for use, in line with NICE's recommendations.

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5 Appraisal Committee members and NICE project team

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 four 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.

Dr Kathryn Abel
Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine/Anaesthesia Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell
Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler
Lay member

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Mary Cooke
Lecturer School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper
GP, St John's Way Medical Centre, London

Professor Peter Crome
Professor of Geriatric Medicine, Bucknall Hospital

Dr Christine Davey
Senior Researcher, North Yorkshire Alliance Research and Development Unit

Richard Devereaux-Phillips
Public Affairs and Reimbursement Manager UK and Ireland, Medtronic

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Stephen Greep
Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Catherine Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Professor Henry Marsh
Consultant Neurosurgeon, St George's Hospital

Professor Gary McVeigh (Vice Chair)
Cardiovascular Medicine, Queens University Belfast and Consultant Physician Belfast City

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Hospital

Dr Eugene Milne
Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers
GP, Helensburgh, Glasgow

Dr Richard Nakielny
Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mrs Ruth Oliver-Williams
Head of Nursing/Quality Improvement Lead Surgical Services, Royal Derby Hospital

Dr Katherine Payne
Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy
Lay member

Dr Martin J Price
Head of Outcomes Research, Janssen-Cilag

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi
Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

John Stevens
Director, Centre for Bayesian Statistics in Health Economics, University of Sheffield

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

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Dr Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman
Health Economics Research Group, Brunel University

Dr Judith Wardle
Lay member

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.

Raphael Yugi
Technical Lead

Eleanor Donegan
Technical Adviser

Laura Malone and Jeremy Powell
Project Managers

Sources of evidence considered by the Committee

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

- Greenhalgh J et al. Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer, October 2009

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). Manufacturers, or sponsors, were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers, or sponsors, professional or specialist and patient or carer groups, and

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other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- Eli Lilly and Company

Professional or specialist and patient or carer groups:

- British Thoracic Society (Lung Cancer and Mesothelioma Working party)
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal College of Physicians' Intercollegiate Lung Cancer Group
- Royal College of Radiologists
- National Lung Cancer Forum for Nurses
- Macmillan Cancer Support
- Roy Castle Lung Cancer Foundation

Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Liverpool Reviews and Implementation Group, University of Liverpool

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- National Coordinating Centre for Health Technology Assessment
- National Collaborating Centre for Cancer

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on Pemetrexed for the maintenance treatment of non-small-cell lung cancer by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Mike Lind, Consultant Medical Oncologist, nominated by the Royal College of Physicians – clinical specialist.
- Dr Paul Bishop, Consultant Histopathologist, nominated by The Royal College of Pathologists – clinical specialist.

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

- Eli Lilly and Company

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Update information

August 2017: Recommendations section updated. Text was removed that said that people who have had pemetrexed in combination with cisplatin as first-line chemotherapy could not have pemetrexed as maintenance treatment. This was done following the publication of NICE's technology appraisal guidance on pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin.

Minor changes since publication

February 2014: Implementation section updated to clarify that pemetrexed is recommended as an option for treating non-small-cell lung cancer.

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