

Pemetrexed for the first- line treatment of non- small-cell lung cancer

Technology appraisal guidance

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1 Guidance

- 1.1 Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.
- 1.2 People who are currently being treated with pemetrexed for NSCLC but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Pemetrexed disodium (Alimta, Eli Lilly and Company Limited) in combination with cisplatin has a marketing authorisation for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology.
- 2.2 Pemetrexed is an antifolate agent that works by disrupting folate-dependent metabolic processes essential for cancer cell replication and survival. Cisplatin is a platinum-based chemotherapeutic agent that has antitumour activity in a number of different cancers.
- 2.3 The licensed dose of pemetrexed is 500 mg/m^2 body surface area, administered as a 10-minute intravenous infusion on the first day of each 21-day cycle. It is followed approximately 30 minutes later by 75 mg/m^2 cisplatin infused over 2 hours. To reduce toxicity, patients treated with pemetrexed should receive folic acid and vitamin B₁₂ supplements. To reduce the incidence and severity of skin reactions, premedication with a corticosteroid is recommended.
- 2.4 Adverse effects commonly associated with pemetrexed include nausea, vomiting, fatigue and leukopenia, particularly in the neutrophil component. Skin rash, mucositis and liver function abnormalities have also been reported. Cisplatin causes nausea and vomiting in the majority of patients. These adverse events are controllable in 50–80% of patients. Serious toxic effects of cisplatin on the kidneys, bone marrow and ears are common, and serum electrolyte disturbances, hyperuricaemia, allergic reactions and cardiac abnormalities have also been reported. For full details of side effects and contraindications, see the summaries of product characteristics.
- 2.5 The cost of pemetrexed is £800 for a 500-mg vial (excluding VAT, 'British national formulary' 57th edition). The cost per patient, assuming an average of four treatment cycles, is approximately £6400. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of pemetrexed and reviews of these submissions by the Evidence Review Group (ERG; [appendix B](#)).

- 3.1 In the submission the manufacturer compared pemetrexed plus cisplatin (pemetrexed/cisplatin) with gemcitabine plus cisplatin (gemcitabine/cisplatin). The manufacturer justified this choice of comparator with marketing data that suggest gemcitabine plus a platinum drug accounts for 80% of first-line NSCLC treatment, and the fact that according to a meta-analysis and clinical opinion cisplatin is the preferred platinum drug. The manufacturer identified gemcitabine plus carboplatin (gemcitabine/carboplatin) and docetaxel plus cisplatin (docetaxel/cisplatin) as additional comparators. The manufacturer stated that carboplatin is still commonly used in the UK because patients do not need the same hydration that is necessary with cisplatin. It also stated that docetaxel is used occasionally because it requires fewer infusions than gemcitabine.
- 3.2 For the comparison of pemetrexed/cisplatin with gemcitabine/cisplatin the manufacturer identified one phase III, open-label, non-inferiority, randomised controlled trial (RCT). This trial (known as JMDB) compared 862 patients given pemetrexed/cisplatin with 863 patients given gemcitabine/cisplatin. It included patients with either squamous or non-squamous NSCLC and subgroups were defined by histology type, including adenocarcinoma, large-cell carcinoma and 'not otherwise specified'. Patients received up to six cycles of chemotherapy and were followed for 2.5 years. The trial results demonstrated overall survival (the primary outcome) of 10.3 months for both pemetrexed/cisplatin and gemcitabine/cisplatin for all randomised patients (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.84 to 1.05, $p = 0.259$). People with NSCLC of non-squamous histology had a greater overall survival with pemetrexed/cisplatin than with gemcitabine/cisplatin, based on median values (11 months versus 10.1 months respectively; HR 0.84, 95% CI 0.74 to 0.96, $p = 0.011$). A subgroup analysis based on median values showed that for patients with adenocarcinoma and large-cell carcinoma, overall

survival was 11.8 months with pemetrexed/cisplatin compared with 10.4 months with gemcitabine/cisplatin (HR 0.81, 95% CI 0.70 to 0.94, $p = 0.005$). A similar subgroup analysis showed that patients with not otherwise specified histology had overall survival of 8.6 months for pemetrexed/cisplatin compared with 9.2 months for gemcitabine/cisplatin (HR 1.08, 95% CI 0.81 to 1.45, $p = 0.586$). The manufacturer concluded that these results together proved the hypothesis that pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin for overall survival in the overall JMDB trial population. It also stated that these results supported targeting pemetrexed/cisplatin treatment to the subgroup of patients with adenocarcinoma and large-cell carcinoma.

- 3.3 The difference in median progression-free survival between patients receiving pemetrexed/cisplatin and gemcitabine/cisplatin in all randomised patients was not significant: 4.8 and 5.1 months respectively (HR 1.04, 95% CI 0.94 to 1.15). In patients with non-squamous histology, median progression-free survival was 5.3 months for pemetrexed/cisplatin and 5.0 months for gemcitabine/cisplatin (HR 0.95, 95% CI 0.84 to 1.06). For the manufacturer's target group of patients with adenocarcinoma and large-cell carcinoma the progression-free survival was 5.3 months for pemetrexed/cisplatin and 4.7 months for gemcitabine/cisplatin (HR 0.90, 95% CI 0.79 to 1.02).
- 3.4 Pemetrexed/cisplatin was associated with statistically significantly fewer grade 3 and 4 adverse events than gemcitabine/cisplatin, specifically neutropenia, febrile neutropenia, thrombocytopenia, anaemia and alopecia. Patients receiving pemetrexed/cisplatin received fewer red blood cell transfusions, and less granulocyte colony stimulating factor and erythropoietin. Patients randomised to pemetrexed/cisplatin experienced statistically significantly more nausea. No quality of life data were measured in the JMDB clinical trial.
- 3.5 The manufacturer carried out an indirect comparison of pemetrexed/cisplatin with other comparators (gemcitabine/carboplatin and docetaxel/cisplatin). The manufacturer identified two phase II, open-label RCTs that could be mapped to the treatment arms of JMDB: Zatloukal et al. (2003) comparing gemcitabine/cisplatin ($n = 87$) with gemcitabine/carboplatin ($n = 89$) and Schiller et al. (2002) comparing gemcitabine/

cisplatin (n = 301) with docetaxel/cisplatin (n = 304). All treatments were administered within their licensed indications. The trials were relatively homogenous in terms of patient population and when compared with the JMDB trial. The manufacturer noted that the unadjusted comparison suggested that median overall survival and progression-free survival were improved in patients with squamous and non-squamous NSCLC who were given pemetrexed/cisplatin relative to the other comparators.

- 3.6 The manufacturer's indirect comparison methodology involved calculating hazard ratios for each of gemcitabine/carboplatin and docetaxel/cisplatin, compared with gemcitabine/cisplatin. The hazard ratios were based on median overall survival and were applied to the hazard rate of the gemcitabine/cisplatin arm in the JMDB trial to produce hazard rates for gemcitabine/carboplatin and docetaxel/cisplatin, adjusted for the JMDB population. This was then used to calculate adjusted median overall survival estimates for the JMDB population. The manufacturer used this method to adjust the hazard rates for the subgroups by using the corresponding hazard rates in JMDB (such as for non-squamous NSCLC). The results of this analysis for the target population of patients with adenocarcinoma and large-cell carcinoma suggested an overall survival advantage for pemetrexed/cisplatin (11.8 months, 95% CI 10.4 to 13.2) versus gemcitabine/carboplatin (9.5 months, 95% CI 8.1 to 13.4) and docetaxel/cisplatin (9.8 months, 95% CI 8.6 to 11.5). Pemetrexed also improved progression-free survival: 5.3 months for pemetrexed/cisplatin compared with 3.8 months for gemcitabine/carboplatin and 4.1 months for docetaxel/cisplatin (no confidence intervals reported).
- 3.7 The manufacturer developed a Markov model with a 6-year time horizon that compared pemetrexed/cisplatin, gemcitabine/cisplatin, gemcitabine/carboplatin and docetaxel/cisplatin. The efficacy data from the JMDB trial were used for the comparison of pemetrexed/cisplatin with gemcitabine/cisplatin, and the results of the indirect comparison were used for the other comparators. The adverse event states were built into the model as separate mutually exclusive health states. All clinical events were modelled via transition probabilities. Treatment effects considered included overall survival, progression-free survival, response rates, adverse events and HRQoL. All effectiveness data used in the model,

apart from HRQoL, were trial-based.

- 3.8 In the model, patients were given a maximum of four cycles of chemotherapy. A continuation rule stipulated that only patients whose disease had responded to pemetrexed/cisplatin after three cycles continued treatment to a fourth cycle. To reflect treatment discontinuation after the third cycle for patients whose disease did not respond, no further chemotherapy costs were incurred.
- 3.9 A literature review of utility data for patients with NSCLC identified a number of studies, but the manufacturer considered that none were suitable for inclusion. Instead, a study by Nafees et al. (2008) was used. This was commissioned to study second-line treatment of NSCLC by the manufacturer, but was assumed by the manufacturer to apply to first-line treatment. It involved 100 members of the public interviewed with visual analogue scale and standard gamble techniques to elicit societal values on utilities in lung cancer.
- 3.10 The base-case analysis compared pemetrexed/cisplatin with gemcitabine/cisplatin. In the population with non-squamous NSCLC, the analysis resulted in an incremental cost of £1364 and 0.041 incremental quality adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) for pemetrexed/cisplatin compared with gemcitabine/cisplatin was £33,065 per QALY gained without the continuation rule (see 3.8). With the continuation rule the incremental cost fell to £1252 and the incremental QALY remained the same, resulting in an ICER of £25,967 per QALY gained. When subgroups according to histology were analysed using the continuation rule, pemetrexed/cisplatin compared with gemcitabine/cisplatin in the adenocarcinoma subgroup gave an ICER of £18,442 per QALY gained, and large-cell carcinoma gave an ICER of £8,056 per QALY gained.
- 3.11 The ERG reviewed the evidence submitted for clinical and cost effectiveness. The ERG report concentrated on the exclusion of vinorelbine, the indirect comparison and the suitability of the chosen cost-effectiveness analysis.
- 3.12 The ERG noted that vinorelbine had been excluded from the analysis

even though the marketing data presented by the manufacturer suggested it accounted for 11% of first-line NSCLC treatment, which was greater than the 4% usage of docetaxel. The ERG considered that vinorelbine should have been included in the manufacturer's decision problem to allow a full assessment of pemetrexed against relevant comparators.

- 3.13 The ERG noted that in the JMDB trial, baseline characteristics were well balanced between treatment arms and between histological subgroups. The ERG noted that the findings from the per-protocol analysis requested from the manufacturer did not differ much from the findings from the intention-to-treat analysis. The ERG considered that this made the JMDB trial results considerably more robust. On request, the manufacturer reported the p values for the test for interaction as $p = 0.0024$ for squamous NSCLC compared with non-squamous NSCLC, and $p = 0.0059$ across all other subgroups. This makes it more likely that there were real differences between the histological subgroups.
- 3.14 The ERG expressed concerns over the trial selection for the indirect comparison. The ERG believed that all the comparators specified in the scope (pemetrexed, docetaxel, gemcitabine, paclitaxel and vinorelbine) should have been included in the indirect comparison analyses. This would have identified five further phase III RCTs for consideration, and improved the subsequent power and validity of the indirect comparison. The ERG also noted that the manufacturer did not assess validity of the included RCTs.
- 3.15 The ERG also expressed concern over the statistical approach used in the indirect comparison. It noted that the manufacturer's method may have resulted in under- or overestimation of treatment effects, and loss of statistical power. It also noted that the manufacturer's submission suggested that the treatment-arm-level hazard rates were used; the ERG stated that indirect comparisons should be based on a comparison of relative effects rather than a comparison of single arm estimates, as the former maintains randomisation within a trial. The ERG stated that the key assumption of an indirect comparison is that the relative effects are exchangeable across the trial settings, that is, there are no treatment effect modifiers. Within the JMDB trial, histology is an effect modifier,

and this should be accounted for in the indirect comparison. The ERG concluded that, because key comparators were excluded from the indirect comparison analysis, and because of the assumptions underlying the statistical approach used, the findings from this analysis should be interpreted with caution.

- 3.16 The ERG commented on the submitted cost-effectiveness analysis. It noted that the chosen Markov model structure did not seem to be appropriate because it did not replicate the trial data, which was used to calibrate the model, to an acceptable level of accuracy. The ERG commented that this was noticeable when calculating response and survival. It considered that because overall survival and progression-free survival were the primary outcomes in the JMDB trial, these two outcomes should be accurately replicated in the economic model for each of the subgroups for the trial period. It noted that the manufacturer's model appeared to overestimate overall survival in both arms and almost all patient groups. For progression-free survival, the ERG commented that the model tended to underestimate in the first 6 months and to overestimate thereafter. In addition, the ERG noted that some survival estimates suggested an error in the model's logic.
- 3.17 The ERG commented on the use of response to treatment in the model structure. It is commonly assumed that response leads to a delay in disease progression and therefore to progression-free survival, this becoming the source of survival gain. Following disease progression it is usually assumed that the natural course of the disease will continue. The JMDB trial data suggested that all the reported survival gain occurred after disease progression, with progression-free survival effectively identical between the pemetrexed/cisplatin and gemcitabine/cisplatin arms. The ERG stated that it was not clear whether objective response determined the extent of health gain and whether the survival gain was restricted to patients whose disease has responded to treatment, or to all patients who had treatment. The ERG considered that this had implications for the design of the model; if response doesn't predict progression-free survival or post-progression survival, then its use as a distinct health state is potentially irrelevant, and could generate misleading results.

- 3.18 The ERG identified other concerns with the cost-effectiveness analysis, including:
- All transition probabilities during the trial period were assumed to arise from constant risk processes (that is, exponential survival distributions), without any justification.
 - A half-cycle correction appeared to have been disabled for costs and used incorrectly for outcomes.
 - Cumulative costs and outcome effects of patients having more than one adverse event at any given time (for example, within a single hospital admission) were not taken into account. This omission could have led to overestimation of the costs and harms attributable to treatment.
 - There may have been an overestimation of mortality because of incorrect use of the febrile neutropenia mortality risk.
- 3.19 The ERG stated that the evidence submitted by the manufacturer was not sufficiently convincing or robust for it to determine the cost effectiveness of pemetrexed.
- 3.20 During the consultation for this appraisal, the manufacturer submitted revised cost-effectiveness estimates for pemetrexed/cisplatin compared with gemcitabine/cisplatin. No other comparators were considered. The primary analysis was a modified version of the previously submitted Markov model, but used Weibull distributions to improve its representation of the outcomes of the JMDB trial. The manufacturer responded to the concerns raised by the Committee concerning the use of response, transition probabilities, half-cycle correction, adverse events and mortality due to febrile neutropenia. It also presented two validation models: a trial-based economic analysis conducted using the individual patient survival outcomes and resource use events from the JMDB clinical trial database, and an economic model used for a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. The PBAC model was based on the patient-level data from the clinical trial and used Weibull distributions to extrapolate survival beyond the trial period. The manufacturer stated that validation processes included a 'double-build' process for the trial-based model (in which two researchers independently built and analysed the database to

make sure data outputs were consistent), and internal and independent external reviews, for both the modified and clinical trial-based models.

- 3.21 The manufacturer's base-case ICER, using the modified Markov model calculated for a maximum of four cycles of treatment, was £27,565 for the population included in the licence (those with non-squamous histology) and £22,202 for patients with adenocarcinoma or large-cell carcinoma. For the trial-based analysis, the ICER calculated for a maximum of four cycles of treatment was £31,157 for the population included in the licence and £24,224 for patients with adenocarcinoma or large-cell carcinoma. When the number of cycles was increased to six, as specified in the trial, the ICERs increased to £42,306 and £33,730 for the two groups respectively. In the PBAC model, the ICER for only four cycles of chemotherapy for patients with adenocarcinoma or large-cell carcinoma was £23,157 per QALY gained.
- 3.22 The ERG commented on the manufacturer's additional analysis. It stated that the cost-effectiveness analyses based on the JMDB trial patient-level data without use of projection techniques were very similar to the previous cost-effectiveness models, and used the same unit cost and state utility parameter values.
- 3.23 However, the ERG noted several limitations with the submitted analyses. These included restricting the number of cycles and corresponding costs, with no corresponding alteration in effectiveness. Therefore, only the estimates using six cycles were valid trial-based estimates. The ERG further noted that new utility values were used in the revised model without explanation. The ERG considered that, as all survival benefit observed for pemetrexed in the JMDB trial occurred after disease progression, the correct utility value for use with the incremental survival is that of the 'progressive disease' state from the original Markov model (that is, 0.47), not that of the pre-progression states of 'stable' (0.65) and 'responding' (0.67).
- 3.24 The ERG noted that the estimates for the cost of chemotherapy did not consider differences in body surface area, or allow for wastage of part-used vials. The ERG suggested that taking these factors into account increased the cost per cycle of pemetrexed/cisplatin chemotherapy by

£81.63 and decreased that of gemcitabine/cisplatin by £3.80.

- 3.25 The ERG noted that the 'in-trial' analysis did not use discounting on either costs or outcomes, despite trial follow-up extending to more than 2 years for some patients. The ERG stated that this was an important omission, because much of the survival gain occurred after the first 12 months and would therefore be likely to be affected by discounting. Drug costs, however, would be incurred early on. The ERG noted that the 'in-trial' analysis used differential costs per patient for terminal care and for best supportive care (BSC). However, these figures were not derived from an analysis of the trial's individual patient data, but were mean results calculated in the manufacturer's Markov model. This created confusion between observation and modelling, which may have distorted the results of the 'in-trial' analysis. The ERG preferred to include terminal care and BSC costs for all patients, but discounted for a period after the recorded survival date for patients censored in the trial.
- 3.26 The combined ERG amendments to the in-trial analysis, using the utility derived from disease progression (0.47) and up to six cycles of chemotherapy, produced an ICER for the population included in the licence of £60,130, and £48,055 for the adenocarcinoma and large-cell carcinoma subgroup.
- 3.27 The ERG noted that the manufacturer's modified Markov model addressed a number of the issues identified by the ERG previously. However, it noted that although the Weibull survival models were better than the original exponential models, they were still not adequate. In particular, they were inaccurate for long-term projection. The ERG also noted that patients having more than one adverse event at a time (for example, during one hospital admission) was not addressed, and chemotherapy costs were based on JMDB trial data and were therefore not representative of UK clinical practice. There was also the issue of reducing six cycles to four, and the effects of this on overall efficacy. In addition the ERG identified new errors in the analysis, including the calculation of adverse event costs, and inappropriate response rates used for the whole population.
- 3.28 The ERG commented that the PBAC health technology assessment

submission was well presented and clearly laid out, thereby simplifying the validation. However, because it was based on the same fundamental assumptions as the manufacturer's Markov analysis, it merely demonstrated that similar assumptions resulted in similar cost-effectiveness results when using a different model structure. The ERG concluded that it did not address some of the major issues with the manufacturer's cost-effectiveness analysis that had been identified previously.

- 3.29 The ERG stated that the time available to review the new evidence submitted by the manufacturer did not allow detailed modifications to be made to the modified Markov model. Instead it used the information contained in the 'in-trial' analysis, together with the additional exploratory survival analysis, to generate modified cost-effectiveness results.
- 3.30 The ERG noted that an extract of individual patient data from the JMDB trial was included by the manufacturer in the 'in-trial' cost-effectiveness analysis. This was restricted to the population of patients with NSCLC and included only information relating to chemotherapy treatment cycles and overall survival, that is, the timing of death or censoring. No information was provided about response to treatment or the time of confirmed disease progression. This data made it possible for the ERG to consider what was the most appropriate estimate of survival gain and utility gain attributable to pemetrexed within the JMDB trial, and thus whether it was possible to estimate the likely change in patient outcomes when treatment was limited to four cycles instead of the maximum of six cycles used in the trial. The ERG classified patients according to the last cycle in which they received a dose of pemetrexed or gemcitabine. Initial examination of Kaplan-Meier survival charts by the ERG indicated that patients could be classified into three groups that were mainly homogeneous with respect to prognosis: up to two cycles, three to four cycles and five to six cycles of chemotherapy. In the absence of specific information on disease progression or treatment discontinuation, these divisions should reflect the approximate time when patients leave the stable or response states. The ERG considered that this analysis provided a basis for considering the possible effects of limiting treatment duration.

- 3.31 The results of the ERG's exploratory analysis suggested that for six cycles of chemotherapy, the ICER for pemetrexed/cisplatin compared with gemcitabine/cisplatin was £28,241 per QALY gained for non-squamous patients and £23,598 per QALY gained for adenocarcinoma and large-cell carcinoma patients. When the number of cycles was reduced to four the ICERs were £20,497 and £17,162 per QALY gained respectively.
- 3.32 The ERG explored two scenarios to account for the potential consequences of reducing the number of chemotherapy cycles. First, if overall survival is related to tumour response, the overall survival gain lost when chemotherapy is stopped sooner can be estimated from the response rate difference (19%). Secondly, if overall survival is related to drug exposure, the overall survival gain lost when chemotherapy is stopped sooner can be estimated as the proportion of treatment cycles given beyond four cycles (32%).
- 3.33 For four cycles of pemetrexed/cisplatin in the population included in the licence (those with non-squamous histology), the exploratory analyses described in 3.32 led to an ICER of £25,336 for a 19% reduction in the overall survival gain, and £30,142 for a 32% reduction in the overall survival gain. For the treatment of patients with adenocarcinoma and large-cell carcinoma subgroup, the respective ICERs were £21,214 and £25,239.
- 3.34 The ERG noted that gemcitabine's patent ended this year (2009), and that generic versions are already being marketed. The ERG explored the potential impact of some market price changes, and noted that they adversely affected the cost-effectiveness estimates for pemetrexed/cisplatin.
- 3.35 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

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 NSCLC and the value placed on the benefits of pemetrexed by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee discussed current UK clinical practice for the treatment of NSCLC. It noted that the manufacturer had limited its analysis to comparisons with gemcitabine/cisplatin, gemcitabine/carboplatin and docetaxel/cisplatin. The Committee heard from clinical specialists that current UK clinical practice was to combine gemcitabine with a platinum drug (usually cisplatin) in the majority of cases. It also heard that there were still some centres that used carboplatin as they could not administer cisplatin because of the hydration required, and possibly because some consider carboplatin to be less toxic.
- 4.3 The Committee discussed the additional comparator presented by the manufacturer (docetaxel/cisplatin) and the ERG's concern that vinorelbine had been excluded. The Committee heard from clinical specialists that docetaxel and vinorelbine are not widely used in the UK because of their adverse-event profiles, in particular the higher rates of febrile neutropenia compared with those seen with pemetrexed and gemcitabine. However, the Committee heard from clinical specialists that docetaxel requires fewer hospital visits than gemcitabine, and so it is occasionally used in areas where patients have difficulty getting to hospital. The Committee noted market research data presented by the manufacturer that confirmed that gemcitabine was the main treatment regimen used in the UK, with an 85% market share. Vinorelbine was in second place with an 11% market share. The Committee heard from clinical specialists that the 11% market share of vinorelbine could be an overestimate because it could include use in other indications. The Committee concluded that the gemcitabine/cisplatin combination was

the principle comparator in UK clinical practice for the first-line treatment of NSCLC.

- 4.4 The Committee considered the evidence on the clinical effectiveness of pemetrexed/cisplatin compared with gemcitabine/cisplatin. It noted that the JMDB trial was well conducted and considered its results to be robust. The Committee heard from the clinical specialists that the histological subtyping was an important factor in predicting response to pemetrexed. It also heard that the improved overall survival with pemetrexed/cisplatin seen in the JMDB trial in the adenocarcinoma and large-cell carcinoma subgroups has been replicated in other studies. Additionally the Committee noted that pemetrexed had not been proven to be effective in the non-specified histology subgroup. It was mindful that the p value for interaction (see 3.13) supported the hypothesis that the differences between the subgroups was real and not due to chance. The Committee concluded that there is evidence to support a true difference in response to pemetrexed between histological subtypes, although the pathophysiological basis for this is not known.
- 4.5 The Committee then discussed whether the results of the JMDB trial were generalisable to UK clinical practice, with particular reference to routine identification of histological subtypes and numbers of treatment cycles recommended. It heard from clinical specialists that histological identification of patients with non-squamous disease to determine whether they have adenocarcinoma or large-cell carcinoma was not common practice in the UK. However the Committee was satisfied that there would not be problems with doing this in practice because pathology services across the UK can perform such histological diagnoses.
- 4.6 The Committee noted that 4 cycles of chemotherapy was considered standard UK clinical practice, whereas the JMDB trial had allowed up to 6, with an average of 4.4 actually being administered. The clinical specialists stated that a reduction in the number of cycles from 4.4 to 4 was unlikely to affect the clinical outcomes of the trial. The Committee concluded that pemetrexed/cisplatin was more clinically effective than gemcitabine/cisplatin in patients with adenocarcinoma and large-cell carcinoma.

- 4.7 The Committee considered the indirect comparison of pemetrexed/cisplatin with gemcitabine/carboplatin and docetaxel/cisplatin. It noted the manufacturer's exclusion of comparators such as vinorelbine. It considered that even though its use in the UK was low, the omission was inappropriate because it excluded additional information and data from the analysis. The Committee was also mindful of the concerns of the ERG over the methodology used by the manufacturer, and of the fact that the indirect comparisons presented in the manufacturer's submission were potentially flawed because of the exclusion of relevant comparators and the chosen statistical method. However, the Committee noted that the gemcitabine/cisplatin combination was the principle comparator in UK clinical practice for the first-line treatment of NSCLC. It also noted evidence from the clinical specialists and patient expert that suggested that gemcitabine/cisplatin was as effective or more effective than gemcitabine/carboplatin or docetaxel/cisplatin. The Committee concluded that its concerns about the indirect comparison did not prevent it from concluding that pemetrexed/cisplatin is clinically effective in UK clinical practice.
- 4.8 The Committee heard from the patient expert and clinical specialists that pemetrexed was valued by patients because of its favourable adverse-event profile, in particular the lower incidences of febrile neutropenia and alopecia. In addition, patients preferred pemetrexed's shorter infusion time and the fewer hospital visits needed for treatment compared with gemcitabine. The Committee concluded that the increased survival in the adenocarcinoma and large-cell carcinoma subpopulations and lower toxicity demonstrated in the JMDB trial for pemetrexed/cisplatin was clinically significant when compared with gemcitabine/cisplatin, especially when taking into account the overall low survival rates for NSCLC.

Cost effectiveness

- 4.9 The Committee considered the manufacturer's original cost-effectiveness analysis and the ERG's critique. The Committee noted that the original model did not replicate the results of the JMDB trial, especially with respect to the three primary clinical outcomes (overall survival, progression-free survival and response rate). The Committee

agreed with the ERG that the model should be able to reproduce the JMDB trial results, because the JMDB trial data are the primary source of clinical data used in the model. The Committee also noted the other problems identified by the ERG and was concerned that the submitted model had not been adequately quality assured. The Committee concluded that on the basis of the evidence presented, the cost effectiveness of pemetrexed/cisplatin had not been proven despite the apparently favourable ICERs in the manufacturer's original submission.

- 4.10 The Committee subsequently considered the revised analysis submitted by the manufacturer. The Committee considered that reducing the number of cycles to four and therefore diverging from the trial was inappropriate for a trial-based analysis. It also considered that the utility values used for progressive states were not appropriate. The Committee concluded that the ERG's exploratory analysis of the manufacturer's revised analysis produced the most plausible estimates. The Committee noted that the ERG's exploratory analysis resulted in ICERs above £48,000 per QALY gained and therefore suggested that pemetrexed/cisplatin was not cost effective. However, the Committee considered that because this analysis only covered the duration of the trial it was inappropriate to conclude cost ineffectiveness from this, although it provided useful additional validation for the subsequently revised Markov model, and the ERG analyses of that.
- 4.11 The Committee considered the manufacturer's modified Markov model and ERG comments on it. The Committee was concerned that some issues of face validity identified by the ERG had not been appropriately addressed. The Committee noted that although reducing the average number of cycles from 4.4 to 4 did not affect the conclusion that pemetrexed was clinically effective, setting a maximum of 4 cycles would affect the conclusions of the cost-effectiveness analysis. It considered that the manufacturer should have taken some account of the probable lower effectiveness. The Committee noted the new errors identified by the ERG that suggested the new analysis had not been sufficiently quality assured. The Committee concluded that the submitted modified Markov model was still not suitable for drawing conclusions because of its inability to replicate the trial results accurately and the lack of quality assurance.

- 4.12 The Committee considered the ERG's exploratory analyses based on the manufacturer's modified Markov model. It was mindful that there were limitations with the data available and that the analyses did not consider the inherent uncertainty in the point estimates through probabilistic sensitivity analysis. The Committee noted that the ERG's estimates of survival were based on individual patient data and that they adequately represented the trial results, in particular the long-term extrapolation. The Committee concluded that the ERG's exploratory analyses were sufficiently robust to allow conclusions to be drawn about the cost effectiveness of pemetrexed/cisplatin.
- 4.13 The Committee noted that the ICERs estimated by the ERG's exploratory analysis were all under £30,000 per QALY gained regardless of the population examined for six cycles of chemotherapy. The Committee noted that when the number of cycles was reduced to four and the ERG's calculations for reduced effectiveness were included, the ICERs were between £20,000 and £30,000 per QALY gained for non-squamous NSCLC and between £17,000 and £25,000 per QALY gained for adenocarcinoma and large cell carcinoma. The Committee therefore concluded that pemetrexed/cisplatin was a cost-effective use of NHS resources based on the evidence available.
- 4.14 The Committee acknowledged that generic versions of gemcitabine have recently become available and that the price was currently subject to change. It noted the ERG's view that when including any substantial price reduction for gemcitabine in the model, pemetrexed/cisplatin was no longer cost-effective compared with gemcitabine/cisplatin. However, it also noted that there was no nationally available price for the generic versions, and that local prices were likely to vary considerably. The Committee concluded that, since the published list price for gemcitabine had not changed, the cost-effectiveness analysis on which it had to base its decision was that described in section 4.13. The Committee considered that the guidance for pemetrexed should be reviewed early if there is a substantial change to the nationally available price of gemcitabine in the NHS.

Conclusion

- 4.15 The Committee considered that current UK clinical practice was to use up to four cycles of gemcitabine/cisplatin as first line-chemotherapy for the treatment of NSCLC. Consequently the Committee considered that the clinical-effectiveness evidence from the JMDB trial, the clinical specialists and patient expert was sufficient and robust enough to demonstrate the clinical effectiveness of pemetrexed/cisplatin in patients with adenocarcinoma and large-cell carcinoma. The Committee noted that pemetrexed/cisplatin had not been shown to be any more effective than gemcitabine/cisplatin in patients with non-squamous NSCLC with unspecified histology. The Committee considered that the ERG's exploratory analysis had demonstrated that the ICERs for pemetrexed/cisplatin were between £17,000 and £25,000 per QALY for adenocarcinoma or large-cell carcinoma. It therefore recommended pemetrexed as an option for the first-line treatment of patients with adenocarcinoma or large-cell carcinoma. The Committee considered that this guidance should be reviewed early if there is any significant change in the price of generic gemcitabine.

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the [NICE website](#). The NHS is not required to fund treatments that are not recommended by NICE.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has non-small-cell lung cancer and the doctor responsible for their care thinks that pemetrexed is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing report and costing template to estimate the savings and costs associated with implementation.
 - Audit support for monitoring local practice.

6 Related NICE guidance

Published

- [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).
- [Pemetrexed for the treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 124 (2007).
- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 24 (2005). [Replaced by [NICE clinical guideline 121](#)]
- [Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer](#). NICE technology appraisal guidance 192 (2010)
- [Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 227 (2011).

Under development

NICE is developing the following guidance (details available from the [NICE website](#)):

- Cetuximab for the treatment of advanced non-small-cell lung cancer. NICE technology appraisal guidance (publication date to be confirmed).

7 Review of guidance

- 7.1 The guidance on this technology was reviewed in January 2012. [Details are on the NICE website.](#)

Andrew Dillon
Chief Executive
September 2009

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

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

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

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

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Mrs Elizabeth Brain

Lay Member

Dr Robin Carlisle

Deputy Director of Public Health, Rotherham PCT

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Mr John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Richard Harling

Director of Health Policy, Worcestershire PCT and Worcestershire County Council

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson

Lay Member

Mrs Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

Mr David Thomson

Lay Member

Dr William Turner

Consultant Urologist, Addenbrooke's Hospital

Dr Luke Twelves

General Practitioner, Ramsey Health Centre, Cambridgeshire

Mr Mike Spencer

General Manager, Cardiff and Vale NHS Trust – Facilities and Clinical Support Services

Dr Jane Adam

Department of Diagnostic Radiology, St George's Hospital

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Mr Christopher Earl

Nurse Advisor, Medicines and Healthcare Products Regulatory Agency

B NICE project team

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

Dr Andres Roman

Technical Lead

Prashanth Kandaswamy

Technical Adviser

Bijal Chandarana

Project Manager

Appendix B: 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, The University of Liverpool:

- Fleeman N, Bagust A, McLeod C, et al. Pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), February 2009

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 (pemetrexed)

II) Professional/specialist and patient/carers groups:

- British Thoracic Oncology Group
- British Thoracic Society (Lung Cancer and Mesothelioma Working party)
- General Practice Airways Group
- Macmillan Cancer Support
- Marie Curie Cancer Care
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians' Intercollegiate Lung Cancer Group

- Royal College of Radiologists

III) Other consultees:

- Department of Health
- Southampton City PCT
- Welsh Assembly Government
- West Sussex PCT

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Liverpool Reviews and Implementation Group, The University of Liverpool
- National Collaborating Centre for Cancer
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- NHS Quality Improvement Scotland
- Sanofi Aventis

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

- Ms Catherine Docherty, Lung Cancer Clinical Nurse Specialist, nominated by Royal College of Nursing – clinical specialist
- Professor David Ferry, Consultant Medical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Dr Jesme Fox, nominated by Roy Castle Lung Cancer Foundation – patient expert

Changes after publication

February 2014: implementation section updated to clarify that pemetrexed is recommended as an option for treating non-small-cell lung cancer. Additional minor maintenance update also carried out.

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

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

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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