

# Pemetrexed for the treatment of malignant pleural mesothelioma

Technology appraisal guidance

Published: 23 January 2008

[www.nice.org.uk/guidance/ta135](http://www.nice.org.uk/guidance/ta135)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

1 Recommendations .....	4
2 Clinical need and practice .....	5
3 The technology .....	7
4 Evidence and interpretation.....	8
4.1 Clinical effectiveness .....	8
4.2 Cost effectiveness.....	10
4.3 Consideration of the evidence .....	14
5 Implementation.....	18
6 Recommendation for further research.....	19
7 Appraisal committee members and NICE project team.....	20
Appraisal committee members .....	20
NICE project team .....	24
8 Sources of evidence considered by the committee .....	25
Update information .....	29

# 1 Recommendations

- 1.1 Pemetrexed is recommended as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate.
- 1.2 Patients currently receiving pemetrexed who do not fall into the patient population defined in section 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

## 2 Clinical need and practice

- 2.1 Malignant pleural mesothelioma (MPM) is a type of cancer that occurs in the pleura – the mesothelium (membranous lining) surrounding the lungs. MPM is a rapidly progressive malignancy of insidious onset.
- 2.2 Approximately 90% of cases of MPM are linked to asbestos exposure. When asbestos fibres are inhaled or swallowed, they can cause scarring of the lung tissues, cancer of the bronchial tree (lung cancer) and sometimes cancers in the pleura and peritoneum. A wide range of occupations, notably shipbuilding, railway engineering and asbestos product manufacture, are associated with an increased risk of MPM. Family members of people whose work clothes were contaminated with asbestos fibres have also developed MPM. The condition is significantly more common in men, with a male to female ratio of 5:1. People with mesothelioma usually present with the disease between the ages of 60 and 79 years.
- 2.3 MPM usually develops 20–50 years after exposure to asbestos. Data from 2004 suggest that about 1700 people in the UK are diagnosed with MPM each year. It is estimated that this figure will increase to a peak of more than 2000 cases each year between 2011 and 2015, reflecting a lag from the highest use of asbestos in the 1970s. An estimated 65,000 cases are expected to occur between 2002 and 2050. The use of asbestos was banned in the UK in 1999.
- 2.4 Most people with MPM present with chest pain and dyspnoea and have pleural effusions evident on examination. Fatigue, profuse sweating, weight loss, anorexia and difficulty in swallowing become common as the disease progresses. Presentation and diagnosis often occur at an advanced stage and the prognosis for most patients is extremely poor. Median survival from diagnosis varies in studies, with a range of 9–13 months. Age, tumour histology, tumour stage at diagnosis and performance status have been shown to be independent prognostic factors. The most commonly used performance status scoring systems include the Karnofsky performance status (KPS) and the World Health Organization (WHO) scales. KPS is a 10-point scale ranging from 0 to 100, with higher scores representing normal day-to-day activity. The WHO system is a five-point scale with lower scores representing normal day-to-day activity. In general,

WHO scores of 0 and 1 are considered equivalent to KPS scores of 70–100.

- 2.5 There is no standard treatment pathway for MPM in England and Wales. The clinical management is multimodal and a patient may receive a combination of treatments. Staging provides prognostic information and can help to determine an appropriate treatment strategy; however, it is complex, and surgical intervention is required to stage the disease fully. There is no universally accepted staging system, but the traditional Butchart system is gradually being replaced with a tumour nodes metastases (TNM) system developed by the International Mesothelioma Interest Group. In clinical practice, MPM is generally staged pragmatically based on whether or not surgical resection is considered an appropriate option. Extrapleural pneumonectomy is an option for the small proportion of patients (1–5%) whose tumours are at stage 1 or 2.
- 2.6 Surgery is not indicated for the majority of patients, so treatment aims to improve symptoms and maintain quality of life for as long as possible. Often, this does not involve treating the tumour with chemotherapy. Treatment that does not include a specific anti-cancer therapy is referred to as active symptom control (ASC) or best supportive care (BSC). For people with MPM, this may include interventions to manage pain and dyspnoea, and to address psychosocial problems. Treatments may include draining excess fluid from the pleural cavity and applying a talc pleurodesis (the insertion of talc to prevent further fluid accumulation), palliative radiotherapy, analgesics, steroids, appetite stimulants and bronchodilators.
- 2.7 There is no standard chemotherapy treatment for MPM. Pemetrexed in combination with cisplatin is the only chemotherapy regimen that is currently licensed for this indication. However, a variety of combination and single-agent regimens such as the mitomycin C, vinblastine and cisplatin combination (MVP) or vinorelbine are used. To date there have been no published randomised controlled trials (RCTs) comparing survival and symptom control in patients receiving chemotherapy with those receiving ASC.

### 3 The technology

- 3.1 Pemetrexed (Alimta, Eli Lilly and Company) is licensed, in combination with cisplatin, for the treatment of chemotherapy-naive patients with unresectable MPM. Pemetrexed is a multi-targeted folate antagonist that inhibits DNA replication. Cisplatin is a platinum-based chemotherapeutic agent that has anti-tumour activity, either as a single agent or in combination, for a number of different cancers. The licensed dose of pemetrexed is 500 mg/m<sup>2</sup> body surface area, to be administered as a 10-minute intravenous infusion on the first day of a 21-day cycle. It is followed approximately 30 minutes later by cisplatin (recommended dose 75 mg/m<sup>2</sup> body surface area) infused over 2 hours. In order to reduce toxicity, patients treated with pemetrexed must receive folic acid and vitamin B<sub>12</sub> supplementation. To reduce the incidence and severity of skin reactions, patients are pre-medicated with a corticosteroid.
- 3.2 Adverse effects commonly associated with pemetrexed include nausea, vomiting, fatigue and neutropenia. Skin rash, mucositis and liver function abnormalities have also been reported. Cisplatin causes nausea and vomiting in the majority of patients. This is controllable in 50–80% of patients with anti-emetic drugs. 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.
- 3.3 Pemetrexed costs £800 for a 500-mg vial (excluding VAT, 'British national formulary' [BNF]53rd edition). The cost per patient, assuming an average of five treatment cycles and a body surface area of 1.8 m<sup>2</sup>, is approximately £8000. Costs may vary in different settings because of negotiated procurement discounts.

## 4 Evidence and interpretation

The appraisal committee considered evidence from a number of sources.

### 4.1 Clinical effectiveness

- 4.1.1 A single RCT of pemetrexed in MPM was identified. The EMPHACIS ('Evaluation of mesothelioma in a Phase III trial of pemetrexed with cisplatin') study compared pemetrexed plus cisplatin with cisplatin alone. This was a single-blind, international, multicentre trial in 448 patients. To be eligible, patients had to be 18 years or older, and were required to have a minimum life expectancy of 12 weeks, uni- or bi-dimensionally measurable disease, and a KPS of greater than or equal to 70. Patients who had had prior chemotherapy, those with a second primary malignancy or brain metastasis, and those unable to interrupt non-steroidal anti-inflammatory drugs were excluded.
- 4.1.2 Patients in the intervention arm (n=226) received pemetrexed at a dose of 500 mg/m<sup>2</sup> followed 30 minutes later by cisplatin at a dose of 75 mg/m<sup>2</sup>. Patients in the control arm (n=222) received normal saline followed 30 minutes later by cisplatin at a dose of 75 mg/m<sup>2</sup>. In both arms, treatment was administered on the first day of each 21-day cycle. The median number of cycles given was 6 (range 1–12) in the pemetrexed plus cisplatin arm and 4 (range 1–9) in the cisplatin arm. Median length of follow-up was 10 months.
- 4.1.3 During the early stages of the trial, incidences of severe toxicity (including drug-related death, neutropenia, febrile neutropenia and diarrhoea) were high in the combination arm. Folic acid and vitamin B<sub>12</sub> supplementation were therefore added to the trial protocol in both treatment arms to preserve blinding. With effect from the date of the protocol change, all patients received supplementation, resulting in three patient subgroups defined by supplementation status: never supplemented (n=70), partially supplemented (those who started treatment before the protocol change; n=47) and fully supplemented (those who started treatment after the protocol change; n=331). The primary analysis was performed on all patients who were randomised and treated (intention-to-treat [ITT] population). A subgroup analysis was performed



on fully supplemented patients. Further post-hoc subgroup analyses were performed on fully supplemented patients with advanced disease (stage 3/4) because it was thought that most patients presenting to clinicians would fall into this category.

- 4.1.4 The primary endpoint of the EMPHACIS trial was survival. A statistically significant survival benefit was observed in patients randomised to pemetrexed plus cisplatin versus those receiving cisplatin alone. In the ITT population, median survival was 12.1 months (95% confidence interval [CI], 10.0 to 14.4) in the pemetrexed plus cisplatin arm versus 9.3 months (95% CI, 7.8 to 10.7) in the cisplatin arm (hazard ratio [HR] 0.77; 95% CI, 0.61 to 0.96; log rank test  $p=0.02$ ). In fully supplemented patients, median survival was 13.3 months (95% CI, 11.4 to 14.9) in the combination arm versus 10 months (95% CI, 8.4 to 11.9) in the cisplatin arm (HR 0.75; 95% CI, 0.57 to 1.00; log-rank test  $p=0.051$ ). In fully supplemented patients with advanced disease, median survival was 13.2 months (95% CI, 9.3 to 14.9) in the combination arm versus 8.4 months (95% CI, 6.8 to 10.2) in the cisplatin arm (HR 0.63; 95% CI, 0.46 to 0.86; log rank test  $p=0.003$ ).
- 4.1.5 Secondary endpoints included 1-year survival, median time to progressive disease and tumour response rate. Pemetrexed plus cisplatin demonstrated statistically significant benefits versus cisplatin alone for all of these outcomes in the ITT population and in the subgroups. The results for these endpoints in the ITT population for the pemetrexed plus cisplatin group versus the cisplatin alone group, respectively, were as follows:
- 1-year survival: 50.3% versus 38.0% ( $p=0.012$ )
  - median time to progression: 5.7 months versus 3.9 months ( $p<0.001$ )
  - tumour response rate: 41.3% versus 16.7% ( $p<0.001$ ).
- 4.1.6 Quality of life was evaluated using the Lung Cancer Symptom Scale–Meso instrument. Several aspects of quality of life were evaluated, including pain, dyspnoea, fatigue, anorexia and cough. Over 18 weeks, patients treated with pemetrexed plus cisplatin demonstrated statistically significant symptomatic improvements when compared with those who received cisplatin alone. For global quality of life in the ITT population, a least squares mean score of 56 out of 100 was reported for patients randomised to pemetrexed plus cisplatin versus a

score of 53 out of 100 for patients in the cisplatin arm (p value for the difference between arms = 0.012). A similar result was observed in the fully supplemented population.

- 4.1.7 Severe to life-threatening or disabling adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone. The most commonly reported of these in patients receiving pemetrexed plus cisplatin were: neutropenia (27.9%), leukopenia (17.7%), nausea (14.6%) and vomiting (13.3%). Supplementation with folic acid and vitamin B<sub>12</sub> resulted in a consistent reduction in the severity and incidence of adverse events (except for dehydration) in the pemetrexed plus cisplatin arm. The most common severe adverse events in fully supplemented patients randomised to pemetrexed plus cisplatin were: neutropenia (23.2%), leukopenia (14.9%), nausea (11.9%) and vomiting (10.7%).
- 4.1.8 Supplementary documentation on pemetrexed provided by the manufacturer indicated that, in the ITT population, 42% (94 of 226) of patients randomised to pemetrexed plus cisplatin responded to treatment. Of those who experienced a response, 87% (82 of 94) did so within four cycles.

## Summary of the evidence on clinical effectiveness

- 4.1.9 The results of the EMPHACIS trial suggest that pemetrexed plus cisplatin confers a survival benefit of approximately 3 months compared with cisplatin alone. The combination treatment also appears to demonstrate advantages in terms of 1-year survival, median time to progressive disease, tumour response rate and quality of life. Pemetrexed plus cisplatin appears to offer greater survival benefits than cisplatin alone in patients with advanced disease.

## 4.2 Cost effectiveness

- 4.2.1 Estimates of cost effectiveness were provided by the manufacturer and by the Assessment Group. A review of the published literature identified a single cost-effectiveness study. This was a conference presentation/abstract that was a forerunner of the manufacturer's submission.

- 4.2.2 Two cost-effectiveness models were submitted by the manufacturer. Model 1 compared pemetrexed plus cisplatin with cisplatin alone. Model 2 compared pemetrexed plus cisplatin with standard care (as defined by the manufacturer on the basis of a market research survey). Both models had a 29-month time horizon (reflecting the trial follow-up period) and took a health service perspective. Both considered outcomes in terms of life years gained and quality-adjusted life years (QALYs). No discounting was applied to costs, because they were all incurred within 1 year. Outcomes were discounted at 3.5%.
- 4.2.3 Model 1 was based on individual patient data from the EMPHACIS trial. The model considered four subgroups: fully supplemented patients; fully supplemented patients with advanced disease; fully supplemented patients with good performance status (WHO performance status of 0 or 1); and fully supplemented patients with advanced disease and good performance status. Data for resource use were taken from the trial and unit costs were taken from Department of Health reference costs or official drug price lists (BNF, MIMS 2005). Mean survival was estimated from the trial data using Kaplan-Meier curves. Utility scores were taken from an ongoing observational study in patients with non-small-cell lung cancer (NSCLC) who completed the EQ-5D health-related quality of life questionnaire before chemotherapy. The base-case utility scores in both economic models were similar for both arms (0.68 for the pemetrexed plus cisplatin arm and 0.69 for the cisplatin alone arm) and did not take account of loss of quality of life in people with MPM as their disease progresses. A range of one-way and two-way sensitivity analyses was performed. No probabilistic sensitivity analysis was performed.
- 4.2.4 The incremental cost-effectiveness ratio (ICER) was £68,598 per QALY gained in the fully supplemented population. The ICER was more favourable in fully supplemented patients with advanced disease (£53,314 per QALY gained), fully supplemented patients with good performance status (£48,099 per QALY gained), and fully supplemented patients with advanced disease and good performance status (£47,567 per QALY gained).
- 4.2.5 Model 2 indirectly compared pemetrexed plus cisplatin with MVP, vinorelbine (with or without platinum) and ASC. Costs and outcomes for pemetrexed plus cisplatin were taken from the fully supplemented population in model 1. For the comparators, resource use data were gathered from market research surveys of

oncologists, commissioned by the manufacturer. Zero cost was assumed for ASC, because it was reasoned that participants in chemotherapy trials would have received a similar level of ASC to patients receiving ASC alone. Median survival estimates were taken from a review of the published literature. Mean values for use in the cost-effectiveness analysis were derived by calculating a weighted average of reported medians and assuming the same mean to median ratio as that observed in the cisplatin only arm of the EMPHACIS trial. The same utility values were used as in model 1, with the utility for cisplatin (0.69) being applied to all comparators in model 2. A range of one-way and two-way sensitivity analyses was performed. The incremental cost per QALY gained for pemetrexed plus cisplatin was calculated to be £21,731 versus MVP, £28,391 versus vinorelbine with or without platinum and £32,066 versus ASC.

- 4.2.6 When the Assessment Group corrected the survival estimate for MVP for performance status, an ICER of £47,972 per QALY gained was obtained for pemetrexed plus cisplatin versus MVP. Using more favourable survival estimates and taking the number of cycles of chemotherapy from the literature rather than the manufacturer's market research survey, the ICERs versus MVP and vinorelbine were both above £60,000 per QALY gained. Using survival estimates for ASC taken from a meta-analysis designed to consider prognostic factors in MPM resulted in an ICER of £48,779 per QALY gained for pemetrexed plus cisplatin versus ASC.
- 4.2.7 The Assessment Group also carried out its own economic analysis of pemetrexed plus cisplatin compared with cisplatin alone. The four subgroups considered in the manufacturer's model 1 were analysed. Mean costs were derived from the individual patient data in model 1. Costs were not discounted. To derive mean effectiveness estimates, Weibull distributions were fitted to the Kaplan-Meier survival curves from the EMPHACIS trial, in order to model the survival distribution of patients at the end of the follow-up period. Mean survival was estimated using the weighted least squares method and a discount rate of 3.5% was applied. In both arms, the Assessment Group used mean utility values of 0.51–0.54 for each subgroup. These values were calculated using an initial utility of 0.65, falling to 0.40 during a 100-day terminal period to account for lower quality of life in people with MPM towards the end of their life.
- 4.2.8 The Assessment Group's analysis resulted in an ICER of £60,600 per QALY

gained in the fully supplemented population. The results were more favourable in fully supplemented patients with advanced disease (£49,100 per QALY gained), fully supplemented patients with good performance status (£50,400 per QALY gained) and fully supplemented patients with advanced disease and good performance status (£37,700 per QALY gained). The Assessment Group also calculated the cost effectiveness of pemetrexed plus cisplatin versus cisplatin alone in fully supplemented patients with advanced disease and good performance status under the assumption that a smaller 100-mg vial of pemetrexed becomes available. In this case the ICER was £34,500 per QALY gained.

- 4.2.9 In a later document, the manufacturer suggested that the ICERs for pemetrexed plus cisplatin might be lower if treatment was stopped in patients who did not experience a tumour response after their fourth cycle. It was suggested that this would lower overall costs without reducing aggregate health benefit, because only those who respond to treatment would experience survival gains. No clinical evidence or economic analysis to support this proposal was submitted.

## Summary of the evidence on cost effectiveness

- 4.2.10 The economic analyses carried out by the manufacturer and the Assessment Group, using model 1, both indicated an incremental cost per QALY gained of greater than £60,000 when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have lower ICERs in patients with advanced disease and/or good performance status. The manufacturer's economic analyses (based on indirect comparisons) using model 2 indicated more favourable ICERs for pemetrexed plus cisplatin when compared with MVP, vinorelbine and ASC. However, the assumptions underpinning model 2 are subject to high levels of uncertainty. When the assumptions were modified to reflect performance-status-adjusted survival, and resource use based on published data, the ICERs from model 2 were in line with those of pemetrexed plus cisplatin versus cisplatin alone.

## 4.3 Consideration of the evidence

- 4.3.1 The committee reviewed the data available on the clinical and cost effectiveness of pemetrexed for the treatment of MPM, having considered evidence on the nature of the condition and the value placed on the benefits of pemetrexed by patient representatives and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The committee heard from clinical specialists and patient experts that pemetrexed plus cisplatin is valued as a potential treatment option in a disease area where it has demonstrated survival and quality of life advantages in an RCT and where there is incomplete evidence on the efficacy of alternative treatments.
- 4.3.3 The committee discussed the relevant comparator for pemetrexed plus cisplatin in the context of the NHS. Clinical specialists advised that cisplatin monotherapy would not normally be used to treat MPM in clinical practice in England and Wales because of a lack of evidence of its effectiveness and its relatively unfavourable adverse-effect profile. The committee heard that there is no standard care pathway for MPM; although some patients receive chemotherapy treatment, notably with MVP or vinorelbine, many patients receive ASC only. However, the committee was also aware that there have been no published RCTs of MVP or vinorelbine in MPM, either versus ASC or against each other. The committee noted that the results of a meta-analysis investigating prognostic factors for MPM suggest that survival with ASC without chemotherapy may be no worse than with chemotherapy. The committee agreed that a direct RCT comparison of the efficacy of pemetrexed plus cisplatin versus other chemotherapy treatments and ASC would be an informative addition to the evidence base.
- 4.3.4 The committee discussed whether pemetrexed should be recommended over treatments for MPM used most frequently in the UK, and therefore considered the indirect comparisons submitted by the manufacturer. It discussed the plausibility of the result that pemetrexed plus cisplatin had lower ICERs when compared with MVP, vinorelbine and ASC than when it was compared with cisplatin alone. The committee noted the high degree of uncertainty surrounding the assumptions underpinning the model and observed that the survival estimates had been taken from relatively small, non-comparative and observational studies. It also noted that the study populations were unlikely to be



comparable with the population of the EMPHACIS trial, particularly in terms of performance status, a key independent predictor of survival in MPM patients.

- 4.3.5 The committee also noted that resource-use estimates for MVP and vinorelbine (based on the number of cycles of chemotherapy derived from the manufacturer's market research surveys) were higher than those reported in the studies from which the effectiveness estimates were taken, and considered the possibility that comparator costs may have been overestimated. The committee saw that when the model assumptions were amended to incorporate more favourable survival estimates and resource use taken from the literature, ICERs were significantly higher. On balance, the committee concluded that it could not base its decision on the indirect comparison model.
- 4.3.6 The committee heard from clinical specialists that cisplatin could be considered a valid chemotherapeutic agent even though it is not favoured in the UK. The committee discussed what could be inferred when the comparative evidence was limited to pemetrexed and cisplatin. It concluded that the survival benefit demonstrated by pemetrexed plus cisplatin in the EMPHACIS trial was likely to be robust because cisplatin was likely to be at least as effective as placebo or ASC, although, in terms of quality of life, cisplatin is likely to have adverse effects. The committee also noted that cisplatin was likely to have higher costs than placebo or ASC and that this would affect the results of cost-effectiveness analysis. The committee discussed the ICERs of pemetrexed plus cisplatin versus cisplatin alone produced by the manufacturer and the Assessment Group, and observed that the range of ICERs was higher than is normally considered acceptable.
- 4.3.7 The committee considered whether it was appropriate to accept economic results expressed in incremental costs per life year gained. The committee noted that the 'Guide to the methods of technology appraisal' advises that the reference case measure of health benefits is the QALY, and that 'where health gain is expressed in terms of life years gained, the range of most plausible ICERs that are acceptable will be substantially lower...' (6.2.6.12). The committee did not consider it plausible that a patient with MPM on chemotherapy would have a full quality of life and this was confirmed by the experts present at the meeting. Furthermore, the committee heard from clinical specialists that utility values derived from studies in NSCLC are a fair approximation of the utility values for people with MPM, and noted that sensitivity analyses indicated the ICERs from

the manufacturer's economic model were not strongly influenced by the utility values. The committee agreed that there are no reasons for it to change its preference for QALYs.

- 4.3.8 The committee discussed the subgroup of patients with both advanced disease and good performance status, in view of the relatively favourable ICERs of pemetrexed plus cisplatin versus cisplatin alone (£37,000 per QALY gained, or £34,500 per QALY gained assuming a 100-mg pemetrexed vial becomes available) that were calculated for this subgroup. The committee was aware that most people with unresectable disease would be considered to have advanced disease and that this subgroup of patients comprised the majority of people with MPM seen in UK clinical practice. The committee accepted that it was plausible that people with good performance status were likely to show a better response to treatment than those with poor performance status.
- 4.3.9 The committee noted that not all patients respond to treatment with pemetrexed plus cisplatin and saw that, in the EMPHACIS trial, 87% of those who responded had done so within four cycles. Furthermore, the committee noted from the consultation that it would be unusual for a UK oncologist to continue treatment beyond four cycles if there was disease progression or no response to treatment. The committee therefore accepted that the mean number of cycles in clinical practice was likely to be less than the mean of six cycles reported in the EMPHACIS trial, and this would result in lower estimates of pemetrexed drug costs.
- 4.3.10 The committee discussed the possibility that differences in symptom relief (including pain and dyspnoea) and quality of life between pemetrexed plus cisplatin and cisplatin alone may not have been captured fully by the economic model because the utilities for both treatment and comparator had been estimated based on data from people with NSCLC. The committee noted that there was some evidence from the EMPHACIS trial showing that pemetrexed plus cisplatin was associated with statistically significant symptomatic improvements (especially with pain relief) compared with cisplatin alone. The committee agreed that the economic analyses may have underestimated the overall quality of life benefits of pemetrexed in people with MPM.
- 4.3.11 Having considered the likelihood of lower numbers of treatment cycles in clinical



practice, the potential availability of a 100-mg pemetrexed vial and the likelihood of greater quality of life benefits than assumed by the cost-effectiveness analyses, the committee agreed that the ICER for pemetrexed plus cisplatin in the fully supplemented subgroup with advanced disease and good performance status was likely to fall within acceptable levels.

- 4.3.12 The committee also noted that MPM is a rare and aggressive malignancy caused by occupational exposure to asbestos and was mindful that this disease has a very poor prognosis.
- 4.3.13 The committee concluded that pemetrexed in combination with cisplatin should be recommended as an option for the treatment of MPM only in people who are considered to have advanced disease and who have a WHO performance status of 0 or 1, in whom surgical resection is not considered appropriate.

## 5 Implementation

- 5.1 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.
- 5.2 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.
- 5.3 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 malignant pleural mesothelioma 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.

## 6 Recommendation for further research

- 6.1 The committee identified a need for RCTs comparing alternative chemotherapy regimens in MPM. Specifically, the committee recommended that trials be conducted in which pemetrexed plus cisplatin is compared with treatments that are currently commonly used in clinical practice in England and Wales in order to determine its relative effectiveness. The committee also recommended that comparative trials of pemetrexed plus cisplatin versus other promising treatments be conducted.

## 7 Appraisal committee members and NICE project team

### Appraisal committee members

The appraisal committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. The appraisal committee meets three times a month except in December, when there are no meetings. The committee membership is split into three branches, each with a chair and 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 Keith Abrams**

Professor of Medical Statistics, University of Leicester

#### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, Radcliffe Infirmary, Oxford

#### **Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

#### **Professor David Barnett**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor Stirling Bryan**

Director of the Health Economics Facility, University of Birmingham

**Mr Brian Buckley**

Vice Chairman, InContact

**Professor John Cairns**

Public Health and Policy, London School of Hygiene and Tropical Medicine

**Professor Mike Campbell**

Statistician, University of Sheffield

**Professor David Chadwick**

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

**Dr Mark Chakravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd

**Dr Peter I Clark**

Honorary Chairman, Association of Cancer Physicians

**Dr Mike Davies**

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

**Mr Richard Devereaux-Phillips**

Public Affairs Manager, Medtronic Ltd

**Professor Jack Dowie**

Health Economist, London School of Hygiene and Tropical Medicine

**Lynn Field**

Nurse Director, Pan Birmingham Cancer Network

**Professor Christopher Fowler**

Professor of Surgical Education, University of London

**Dr Fergus Gleeson**

Consultant Radiologist, Churchill Hospital, Oxford

**Ms Sally Gooch**

Former Director of Nursing & Workforce Development, Mid Essex Hospitals Services NHS Trust

**Mrs Barbara Greggains**

Lay Member

**Mr Sanjay Gupta**

Former Stroke Services Manager, Basildon and Thurrock Universities Hospitals NHS Trust

**Professor Philip Home**

Professor of Diabetes Medicine, University of Newcastle upon Tyne

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Professor Peter Jones**

Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

**Dr Mike Laker**

Medical Director, Newcastle Hospitals NHS Trust

**Dr George Levvy**

Lay Member

**Ms Rachel Lewis**

Nurse Adviser to the Department of Health

**Mr Terence Lewis**

Mental Health Consultant, National Institute for Mental Health in England

**Professor Jonathan Michaels**

Professor of Vascular Surgery, University of Sheffield

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queen's University, Belfast

**Dr Ruairidh Milne**

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

**Dr Neil Milner**

General Medical Practitioner, Tramways Medical Centre, Sheffield

**Dr Rubin Minhas**

General Practitioner, CHD Clinical Lead, Medway PCT

**Dr John Pounsford**

Consultant Physician, North Bristol NHS Trust

**Dr Rosalind Ramsay**

Consultant Psychiatrist, Adult Mental Health Services, Maudsley

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Mr Cliff Snelling**

Lay Member

**Mr Miles Scott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Dr Ken Stein**

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

## 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.

**Ebenezer Tetteh**

Technical Lead

**Janet Robertson**

Technical Adviser

**Reetan Patel**

Project Manager



## 8 Sources of evidence considered by the committee

A. The assessment report for this appraisal was prepared by Liverpool Reviews & Implementation Group, University of Liverpool. Dundar Y, Bagust A, Dickson R et al. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation (December 2005)

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report, and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Eli Lilly and Company

II) Professional/specialist and patient/carer groups:

- Asbestos Awareness Wales/UK
- Asbestos Diseases UK
- Association of Cancer Physicians
- Association for Palliative Medicine of Great Britain
- British Mesothelioma Interest Group (BMIG)
- British Oncology Pharmacy Association
- British Psychosocial Oncology Society
- British Thoracic Society (Lung Cancer and Mesothelioma Working party)
- Cancerbackup
- Cancer Research UK

- Cancer Voices
- June Hancock Mesothelioma Research Fund
- Long Term Medical Conditions Alliance
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Palliative Care
- National Lung Cancer Forum for Nurses
- Occupational and Environmental Diseases Association
- Ridings Asbestos Support and Awareness Group (RASAG)
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing
- Royal College of Physicians' Intercollegiate Lung Cancer Group
- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal Pharmaceutical Society
- Society of Cardiothoracic Surgeons of Great Britain and Ireland
- Society of Radiographers
- Tenovus Cancer Information Centre

III) Commentator organisations (without the right of appeal):

- Approved Prescription Services (cisplatin)
- Bristol-Myers Squibb Pharmaceuticals (cisplatin)
- British National Formulary

- British Thoracic Oncology Group
- GMB Union
- Institute of Cancer Research
- Liverpool Reviews and Implementation Group
- Mayne Pharma (cisplatin)
- MRC Clinical Trials Unit
- National Cancer Research Institute
- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Transport & General Workers Union
- Welsh Assembly Government

C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the appraisal committee discussions and provided evidence to inform the appraisal committee's deliberations. They gave their expert personal view on pemetrexed for malignant pleural mesothelioma by attending the initial committee discussion and/or providing written evidence to the committee. They were also invited to comment on the ACD.

- Dr Mary O'Brien, Consultant Medical Oncologist, Institute of Cancer Research, nominated by the Institute – clinical specialist
- Dr Robin Rudd, Consultant Physician, British Thoracic Society, nominated by the British Thoracic Society – clinical specialist
- Ms Liz Darlison, Consultant Nurse, Mesothelioma UK, nominated by June Hancock Mesothelioma Research Fund – patient expert

- Macmillan Lung Nurse Specialist, Harrogate District Hospital, nominated by June Hancock Mesothelioma Research Fund  
– patient expert

# Update information

## Minor changes since publication

**March 2014:** Implementation section updated to clarify that pemetrexed is recommended as an option for treating malignant pleural mesothelioma.

ISBN: 978-1-4731-5675-3