Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin

Technology appraisal guidance
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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 are 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.

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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.
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1 Recommendations

1.1 Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer in adults when:

- their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy
- their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment and
- the company provides the drug according to the terms of the commercial access agreement as agreed with NHS England.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 This guidance is not intended to affect the position of patients whose treatment with pemetrexed was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
## The technology

| Description of the technology | Pemetrexed (Alimta, Eli Lilly and Company) is a multi-targeted anticancer antifolate agent that disrupts crucial folate-dependent metabolic processes essential for cell replication. |
| Marketing authorisation | Pemetrexed has a marketing authorisation as 'monotherapy for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy'. |
| Adverse reactions | The most common adverse reactions of pemetrexed are bone marrow suppression; anaemia, neutropenia, leukopenia, thrombocytopenia, and gastrointestinal toxicities; anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. For full details of adverse reactions and contraindications, see the summary of product characteristics. |
| Recommended dose and schedule | The recommended dose of pemetrexed is 500 mg/m² of body surface area; it is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. To reduce toxicity, patients should also receive folic acid and vitamin B12 supplements. To reduce the incidence and severity of skin reactions, premedication with a corticosteroid is recommended. |
| Price | The list price for pemetrexed is £160 for a 100 mg vial and £800 for a 500 mg vial (excluding VAT; 'British national formulary' [BNF] January 2014). Using the company’s estimated average body surface area of 1.79 m² the drug cost for each treatment cycle is £1,440. Because treatment continues until disease progression or toxicity, the number of cycles varies; in the clinical trial the mean number of cycles for maintenance treatment was 7.86. Therefore, assuming 8 cycles of treatment, the average total treatment cost is approximately £11,520. The company has agreed a commercial access agreement with NHS England that makes pemetrexed available at a reduced cost for continuation maintenance treatment (that is, pemetrexed maintenance after pemetrexed and cisplatin induction therapy). The financial terms of the agreement are commercial in confidence. |
3 Evidence

The appraisal committee (section 6) considered evidence submitted by Eli Lilly and Company and a review of this submission by the evidence review group (ERG). This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. It focused on cost-effectiveness analyses using a commercial access agreement, which provides pemetrexed at a reduced cost for continuation maintenance treatment (that is, pemetrexed maintenance after pemetrexed and cisplatin induction therapy). The financial terms of the agreement are commercial in confidence. See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE’s original technology appraisal guidance on pemetrexed maintenance treatment after induction therapy with pemetrexed and cisplatin.
Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of pemetrexed, having considered evidence on the nature of non-squamous non-small-cell lung cancer (NSCLC) and the value placed on the benefits of pemetrexed maintenance treatment after pemetrexed and cisplatin induction therapy by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee was aware of comments received from a patient group describing the limited life expectancy of people with NSCLC and of the importance to patients and their families of the availability of additional active therapy options. The committee was also made aware of the most common symptoms experienced by people with NSCLC including breathlessness, persistent cough, weight loss, listlessness and fatigue.

Scope of the appraisal

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

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

4.4 The committee discussed performance status in relation to both first-line chemotherapy for advanced non-squamous NSCLC and maintenance treatment. It noted that NICE’s guideline on lung cancer recommends that:

- chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (World Health Organization [WHO] 0, 1 or a Karnofsky score of 80–100)

- chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug, the latter being either carboplatin or cisplatin and

- patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.

The committee heard from clinical experts that in clinical practice most patients potentially eligible for chemotherapy for advanced NSCLC have a performance status of 0 or 1 rather than a performance status of 2. However, whereas most patients with advanced non-squamous NSCLC with a performance status of 0 or 1 receive palliative chemotherapy, a much smaller proportion of patients with a performance status of 2 receive chemotherapy. The clinical experts indicated that whereas the combination of cisplatin and pemetrexed would only be used for patients with a performance status of 0 or 1, carboplatin-based chemotherapy was also used for this group too, as well as for patients with a performance status of 2. The clinical experts also pointed out that maintenance pemetrexed would be considered for use in any patients with a performance status of 0 or 1 at the end of first-line chemotherapy whatever their performance status at the start of first-line chemotherapy. The committee heard from the company that although the summary of product characteristics does not specify a patient’s performance status in the wording of the maintenance indication (see section 4.1 of the summary of product characteristics), it does refer to patients in the maintenance trials as having a performance status of 0 or 1 in section 5.1. The company therefore considered that treating NSCLC in patients with a performance status other than 0 or 1 would be outside the licensed indication for maintenance pemetrexed. The committee concluded that although the licensed indication does not specify performance status for maintenance pemetrexed, it would not be usual clinical practice for a patient with a performance status other
than 0 or 1 to receive pemetrexed maintenance treatment after induction therapy with pemetrexed plus cisplatin.

Clinical effectiveness

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

4.6 The committee discussed the number of pemetrexed maintenance cycles that a patient would be likely to receive, conscious of the evidence review group's (ERG's) comment that the mean number of cycles of treatment with pemetrexed in PARAMOUNT was more than 7 cycles and that 6 cycles might be considered a likely maximum in UK clinical practice. However, the committee heard from clinical experts that patients would have treatment until disease progression or unacceptable toxicity, or patient or physician choice to stop treatment early, rather than with a set number of cycles. Based on the evidence put forward by the clinical experts, the committee concluded that patients would receive pemetrexed maintenance treatment until disease progression or unacceptable toxicity.

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

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

Cost effectiveness

4.9 The committee considered the assumptions around resource use in the economic model submitted by the company. It first discussed the monitoring requirements for pemetrexed maintenance treatment. The committee was aware that patients in PARAMOUNT had a CT scan every 6 weeks, and heard from clinical experts that a CT scan would be repeated every 2 to 3 months during maintenance treatment in UK clinical practice. The committee noted the company’s original assumption that 3% of patients would need additional scans, occurring every 24 weeks. The committee noted that the revised base case and the updated revised base case provided by the company increased the proportion of patients needing additional scans to 100% and increased the frequency of CT scans to once every 12 weeks. Based on the clinical experts’ comments, the committee concluded that this was an acceptable assumption.

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

4.11 The committee welcomed the company’s revisions to its base case and updated revised base case but noted that some concerns remained about concomitant medication costs, utility model design and survival projection. The committee discussed the absence of the cost of the concomitant medications that are needed with pemetrexed (vitamin supplements and dexamethasone) in the company’s revised and updated revised base-case analyses. The committee heard from the company that a free ‘supplementation pack’ that includes vitamins and dexamethasone had been introduced to hospitals in the UK. The committee was aware that the impact on the incremental cost-effectiveness ratio (ICER) of including the concomitant medication costs was small (around £100). The committee concluded that the effect on the ICER of including the concomitant medication costs was not significant, particularly when compared with the other outstanding issues, and so did not need to be considered further.

4.12 The committee considered the method used for estimating utility in the economic model. It heard from the company that its preferred method of estimating utility was the unadjusted mixed model based on the PARAMOUNT EQ-5D individual patient data because it gave intuitive utility values. The committee agreed that the values were intuitive but remained concerned that including a cycle variable to account for changes in utility with treatment cycles in the adjusted model would cause significant instability. The committee discussed the alternative utility values from the Nafees model, and was aware that these were based on patients with NSCLC receiving second-line treatment, rather than maintenance treatment. In addition, the committee had reservations about using the Nafees utility values (which were not obtained using EQ-5D methods) in preference to EQ-5D data from PARAMOUNT. The committee welcomed the availability of EQ-5D data from the trial and agreed that they should be used to provide the utility values for the model. However, the committee remained cautious about how the unadjusted regression model had explored the effect of treatment on utility. Furthermore, the committee was aware that to accommodate the impact of a loss in utility (disutility) from an adverse effect of treatment, the company had calculated an average disutility for all pre- and post-progression health states, and applied these to the pre-progression health states only. Although the committee accepted that
disutility from treatment-related adverse reactions would only occur during the
pre-progression phase (while a patient is still on treatment), it was not
appropriate that the disutility value should be estimated from an average of the
on-treatment and off-treatment times. The committee concluded that although
the unadjusted model had not been optimally executed and disutility had not
been correctly estimated, the values were still preferable to those from the
Nafees model, which were neither EQ-5D based nor from the population of
interest.

4.13 The committee discussed the source of resource use data within the economic
model used to calculate the cost of adverse reactions. It was aware that the
economic model allowed 2 methods for calculating resource use, the company's
preferred approach, 'JMEN method', and the ERG's preferred approach,
'PARAMOUNT'. The committee understood that the PARAMOUNT method
used data directly from PARAMOUNT and was not limited to including only
4 adverse reactions. It agreed with the ERG that the more detailed
PARAMOUNT approach was reasonable. The committee concluded that it was
more appropriate to use the PARAMOUNT method because this did not limit
the adverse reactions included and was more detailed.

4.14 The committee considered the evidence in support of a post-progression
benefit of pemetrexed over placebo. The committee noted the ERG's
Kaplan–Meier analysis of post-progression survival indicated that for the 2 trial
arms, survival corresponded very closely. The committee also understood from
comments made by the clinical experts at the first committee meeting that a
continued benefit of pemetrexed over best supportive care after disease
progression is difficult to explain. The committee heard from the company that
it was not considered plausible that a patient would receive a benefit from
pemetrexed throughout treatment and that the benefit would suddenly stop
immediately on discontinuation of treatment. However the committee noted
that although it may not be plausible to assume an immediate end to the benefit
of treatment on disease progression, this was not the same as assuming a
significant benefit of pemetrexed over and above that of placebo. During
consultation the company highlighted Stein et al. (2009) and Stein et al. (2011)
as evidence of treatment effect reducing tumour growth rates after treatment is
stopped (using non-pemetrexed treatments) in patients with advanced prostate
and renal cancer. The committee considered that the findings in these papers
did not support an extended benefit of chemotherapy after disease progression,
because the only scenario in which post-treatment benefit was suggested occurred with a vaccine treatment. The committee did not find any reason for basing its decision on anything other than the PARAMOUNT data, which did not show any evidence for a post-progression benefit of pemetrexed over placebo. The committee concluded that no evidence to support a post-progression benefit for pemetrexed over placebo had been provided throughout the appraisal.

4.15 The committee further discussed the approaches to survival modelling. It noted that the company had challenged the committee's review of the ERG's modelling approach, suggesting that the ERG should have done statistical tests, such as goodness of fit. The committee suggested to the company that, in the single technology appraisal process, the onus is on the company to provide the evidence, including an economic model. It considered that the ERG's role is to critique the evidence, rather than build a new model. The committee heard that the company agreed that this is the case but still considered that the committee should have commented more specifically on the company's supporting statistical tests, which the company considered to provide justification for the use of the gamma distribution to project overall survival. The committee then heard from the ERG that additional statistical tests were not necessary because, in the ERG's opinion, the PARAMOUNT data were sufficiently mature to allow calculation of the survival advantage of pemetrexed without any extrapolation. This was because the trajectories of the pemetrexed and placebo curves were parallel and could be overlaid once overall survival was less than about 37% by shifting the overall survival curve of the control arm to the right by approximately 200 days. This approach allowed the difference in survival to be calculated from the differences in areas under the curves, and was approximately 106 days (3.49 months). The committee understood from the ERG that this approach removed the need to use a hazard function to model the survival data, and was based on a new exploration of data that the company had previously provided, and that had been available throughout the course of the appraisal. After further discussion, the company agreed that there appeared to be no statistically significant difference in post-progression survival between the trial groups. The committee concluded that extrapolation of the data was not needed and that its decision on the cost effectiveness should be made based on the actual data.
Based on its discussions (see sections 4.12–4.15), the committee considered that the most appropriate ICER should be calculated using the revised assumptions about cost and resource use, the unadjusted utility model and the ERG’s approach to survival modelling. The result of combining these assumptions was confirmed by the ERG to produce an ICER of approximately £74,500 per quality-adjusted life year (QALY) gained.

**End-of-life considerations**

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

- Treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7,000 for all licensed indications in England.

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

Noting evidence from the National Lung Cancer Audit (2013) and the survival time of patients on placebo and best supportive care in PARAMOUNT, the committee concluded that the life expectancy of patients with advanced non-squamous NSCLC is normally less than 24 months. For the criterion about extension to life, the committee noted the results from PARAMOUNT showing that there was a statistically significant increase in median overall survival of 2.85 months for pemetrexed compared with best supportive care. Although this was not greater than 3 months, the committee was aware that all of the modelled estimates provided by the company and the ERG were greater than 3 months. The committee therefore concluded that there was sufficient
evidence to indicate that the treatment offers extension to life of at least 3 months.

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

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

4.20 The committee discussed the small patient population criterion. It heard from NICE that, for treatments for small groups of patients, higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product if the licensed indications only apply to a small potentially eligible patient population. It further heard that the case for reduced cost effectiveness weakens as the potential total population for a product increases. Therefore, taking into account the cumulative population covered by all the indications in the marketing authorisation needs to be considered. The committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation. The committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them based on actual use. As advised by NICE, the committee considered that the calculation of the total population should reflect only the population covered by the licensed indications in the countries where NICE guidance has formal effect (since April 2013, that is England, rather than England and Wales). The committee recognised that in the case of patients having first-line chemotherapy with pemetrexed plus cisplatin and then continuing on maintenance pemetrexed, this
represented additional opportunities for the company to recoup the costs of development for pemetrexed.

4.21 The committee considered the population size for pemetrexed as first-line therapy. It was aware that the licensed indication is that pemetrexed should be given in combination with cisplatin, and, based on comments from the clinical experts, that only patients with a performance status of 0–1 would be considered for treatment with cisplatin. However, for patients who are fit enough to tolerate this combination, the committee heard from the clinical experts that this would be the first-line treatment of choice. The committee noted that, according to the National Lung Cancer Audit (2013), the number of patients in England with confirmed NSCLC who have a performance status of 0–1 and who have stage IIIB or IV disease is 6,735. It understood that 68% of these patients would have non-squamous histology (see NICE's guideline on lung cancer), therefore the potential population eligible for first-line therapy with pemetrexed would be 4,580. The committee was aware of comments received during consultation suggesting that this figure included a number of people with lung cancer that is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation positive and that in clinical practice; these people would not receive pemetrexed. The committee discussed this comment but was of the opinion that it is appropriate to estimate the potential population as defined by the licensed indication. The committee was aware that the decision to estimate the potential population as defined by the licensed indication, rather than actual use, was in line with an appeal panel decision for erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer. The committee concluded that the population to be included in the calculations for first-line treatment was therefore 4,580.

4.22 The committee considered the population size for the maintenance indication for pemetrexed. It was aware that the licence extension meant that pemetrexed would be an option for patients as ‘continuation maintenance’ (that is, pemetrexed maintenance treatment after induction therapy with pemetrexed plus cisplatin) or ‘switch maintenance’ (that is, pemetrexed maintenance treatment after induction therapy that does not include pemetrexed). The committee noted that the National Lung Cancer Audit (2013) reported that, of those eligible for first-line treatment (4,580), 57.2% (2,620) receive first-line chemotherapy and of these 40% (1,048) receive pemetrexed plus cisplatin. Of these, the company estimated that 58.4% (612) would be eligible for
pemetrexed continuation maintenance treatment. The committee accepted this number. For switch maintenance, the committee noted the comments received during consultation, which suggested that pemetrexed would either be used in a first-line setting or as switch maintenance, but not as both. The committee found the comments received about switch maintenance to be reasonable and therefore decided that it was not appropriate to account for switch maintenance treatment in addition to first-line treatment. The committee concluded that the population to be included in the calculations for maintenance treatment was therefore 612.

4.23 The committee considered the population size for the second-line treatment of NSCLC for pemetrexed. It noted that anyone who did not receive pemetrexed as induction or maintenance therapy (that is, those patients with a performance status of 2) would be potentially eligible for second-line pemetrexed therapy after disease progression. It noted the company’s most recent estimate that 429 people in England and Wales receive first-line chemotherapy that does not include pemetrexed, and that of this group an estimated 20% of people will die before disease progression, leaving a potential second-line treatment population of about 340. The committee agreed that including patients who had died would be perverse and that they should not be included in the total population size. The company then further refined the estimate of 340 by performance status, resulting in an estimate that 180 patients in England and Wales with a performance status of 2 would be eligible to receive pemetrexed in a second-line setting. The committee did not accept that the population should be reduced according to performance status, preferring instead to estimate the population size based on the licensed indication (which does not restrict treatment by performance status). Aware that the population size should be based on the population in England alone (rather than England and Wales) the committee accepted a further adjustment based on data contained in the National Lung Cancer Audit (2013), reducing the estimated number who would be eligible for pemetrexed as per its licensed indication in a second-line setting from 340 to 320 people. The committee concluded that the population to be included in the calculations for second-line treatment was therefore 320.

4.24 The committee was aware that pemetrexed also has a marketing authorisation for mesothelioma. The committee noted that, according to the National Lung Cancer Audit (2013), the number of patients with mesothelioma in England and Wales is 1,964. Aware that the population figures should be based on the
population in England alone (rather than England and Wales) the committee reduced the number of mesothelioma patients from 1,964 to 1,872 based on data from a Cancer Research UK report from 2010. The committee understood that 88% of these patients would have advanced disease; therefore the potential population with mesothelioma eligible for pemetrexed would be 1,647. The committee was aware of comments received during consultation suggesting that the mesothelioma population eligible for pemetrexed should be limited to those patients with a performance status of 0–1. However, in line with its previous discussions about the licensed population (rather than the eligible population; see sections 4.21 and 4.23), the committee considered it was appropriate to estimate the potential population, as defined by the licensed indication. The committee concluded that the population to be included in the calculations for mesothelioma treatment was therefore 1,647.

4.25 The committee considered the total population size for which pemetrexed has a licence (approximately 7,160). The committee was of the opinion that this figure estimated the maximum population size of patients who could receive pemetrexed for its licensed indications in England. Therefore, the committee was persuaded that the population eligible for pemetrexed would not be higher than this figure. The committee considered the population size in the context of the other end-of-life criteria for this appraisal (see section 4.18). It acknowledged that the benefit of pemetrexed had been demonstrated in all modelled estimates of mean overall survival, and that pemetrexed therefore offered a valuable treatment option for a population of people for whom no other treatment options existed at this maintenance stage. It further considered that the estimate of the population size was very close to 7,000 (see NICE’s guide to the methods of technology appraisal). Taking these 2 factors into consideration, the committee concluded that the total patient population should be considered as a small population for the purposes of meeting the criterion for the supplementary advice on end of life. The committee therefore concluded overall that pemetrexed maintenance treatment after induction therapy with pemetrexed and cisplatin could be considered under the supplementary advice to the committee on end-of-life treatments.

4.26 The committee noted that even taking into account end-of-life considerations, all the estimates of the ICER (including the one the committee felt represented the most plausible ICER, that is, approximately £74,500 per QALY gained) for pemetrexed maintenance treatment after induction therapy with pemetrexed
and cisplatin were substantially higher than would normally be considered a
cost-effective use of NHS resources. Therefore the committee concluded that
pemetrexed maintenance treatment should not be recommended for treating
locally advanced or metastatic non-squamous NSCLC in people whose disease
has not progressed immediately after induction therapy with pemetrexed and
cisplatin.

4.27 The committee discussed whether its recommendations for pemetrexed as a
maintenance therapy after induction with pemetrexed plus cisplatin were
associated with any issues related to equality legislation and the requirement
for fairness. The committee was aware that NICE's technology appraisal
guidance on pemetrexed recommends it as an option for the maintenance
treatment of locally advanced or metastatic NSCLC other than predominantly
squamous cell histology if disease has not progressed immediately after
platinum-based chemotherapy plus gemcitabine, paclitaxel or docetaxel. The
committee discussed whether its recommendations could be considered unfair
given the recommendations in NICE's technology appraisal guidance on
pemetrexed, and that the difference between the populations in that appraisal
and the current appraisal was in terms of the first-line treatment received. The
committee agreed that first-line treatment is not linked to the protected
characteristics covered in the equality legislation. The committee was aware
that it needs to make a decision for each appraisal based on the evidence before
it and this is what it has done in this case. The committee agreed that its decision
on pemetrexed as a maintenance therapy after induction with pemetrexed plus
cisplatin was made because pemetrexed maintenance was not cost effective in
this population. Furthermore, even if there was any unfairness, given the high
ICER of approximately £74,500 per QALY gained, the committee agreed that
the recommendation could be justified and was in line with the committee's role
and the application of the cost-effectiveness criteria, and was a proportionate
means of achieving a legitimate aim. The committee had not identified any
special factors that would require or justify making a positive recommendation
despite the very high ICER.

4.28 The committee discussed an issue raised by the company that a negative
recommendation for pemetrexed as a maintenance treatment after induction
therapy with pemetrexed and cisplatin would amount to a withdrawal of the
treatment when it appears to be working. The committee noted that the first-
line and maintenance indications for pemetrexed are separate; that they have
been supported by separate trial development programmes and that they are considered to be separate stages of treatment, especially since the first-line indication specifies that pemetrexed is given with cisplatin whereas the maintenance indication specifies that pemetrexed is given as a monotherapy. The committee did not therefore accept the company's assertion that there would be an ethical implication to a decision not to recommend pemetrexed as a maintenance treatment after induction therapy with pemetrexed and cisplatin.

**Cancer Drugs Fund reconsideration**

4.29 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. The committee considered the updated company submission and cost–utility analysis that included:

- a commercial access agreement
- the revised assumptions about cost and resource use and
- the unadjusted utility model.

The committee noted that the commercial access agreement covered people whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and whose Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 at the start of maintenance treatment. It agreed that this was in line with both PARAMOUNT and clinical practice (see section 4.4). The committee acknowledged that the company was unable to use the ERG's approach to survival modelling without major restructuring of its model, but had considered the effect this would have on the ICER by adding the difference obtained using the 2 methods to the resulting ICER. The ERG did exploratory analyses using their approach to survival modelling, updating drug costs, and accounting for NHS cost inflation since the original appraisal. The resulting ICERs were similar to those produced by the company. The ICERs incorporating the commercial access agreement are commercial in confidence.
End-of-life considerations

4.30 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. It noted the committee's previous conclusion that the end-of-life criteria had been met (see sections 4.18–4.25) and that the criterion that the treatment is licensed or otherwise indicated for small patient populations is no longer relevant. The committee therefore considered the end-of-life criteria to be fulfilled.

Overall conclusion

4.31 Given the new cost-effectiveness analysis, including the commercial access agreement, and considering the end-of-life criteria, the committee recommended pemetrexed maintenance treatment as a cost-effective use of NHS resources for people whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and whose Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 at the start of maintenance treatment.

Equality issues

4.32 The committee considered whether its recommendations were associated with any potential issues related to equality. The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

Summary of appraisal committee's key conclusions

<table>
<thead>
<tr>
<th>TA402</th>
<th>Appraisal title: Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion (Cancer Drugs Fund reconsideration of TA309)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer in adults when:

- their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy
- their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment and
- the company provides the drug according to the terms of the commercial access agreement.

The committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer (NSCLC) in patients whose disease has not progressed immediately after induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.

Given the new cost-effectiveness analysis submitted for the Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance, including the commercial access agreement, and considering the end-of-life criteria, the committee recommended pemetrexed maintenance treatment as a cost-effective use of NHS resources for people whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and whose Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 at the start of maintenance treatment.

Current practice (TA309)

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The committee heard from a patient group about the importance to patients and their families of the availability of additional active therapy options.</th>
</tr>
</thead>
</table>

The technology (TA309)
### Proposed benefits of the technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

The committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately after induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.

### What is the position of the treatment in the pathway of care for the condition?

Pemetrexed has a marketing authorisation as ‘monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy’.

### Adverse reactions

The committee concluded that treatment with pemetrexed maintenance therapy was associated with clinically significant but acceptable adverse reactions.

### Evidence for clinical effectiveness (TA309)

#### Availability, nature and quality of evidence

The only evidence of clinical effectiveness came from 1 randomised clinical trial (PARAMOUNT). The committee considered that PARAMOUNT was well designed.

#### Relevance to general clinical practice in the NHS

The committee concluded that the patients in the PARAMOUNT trial were generally fitter and younger than those seen in clinical practice in England.

#### Uncertainties generated by the evidence

The committee concluded that the patients in the PARAMOUNT trial were generally fitter and younger than those seen in clinical practice in England.
<table>
<thead>
<tr>
<th>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</th>
<th>No clinically relevant subgroups were identified during the appraisal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The committee concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately after induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.</td>
</tr>
</tbody>
</table>

**Evidence for cost effectiveness (TA309)**

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The company submitted a state-transition Markov model to evaluate the cost effectiveness of pemetrexed compared with placebo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The committee was not persuaded by the company's approach to the modelling of progression-free survival and overall survival. The committee also concluded that more accurate estimates of resource use and utility parameters were available than those used in the company's revised base case.</td>
</tr>
<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>No significant and substantial health-related benefits that have not been captured by the QALY calculation were identified either in the submission or at the committee meeting.</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>No clinically relevant subgroups were identified during the appraisal.</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The different approaches to estimating overall survival for the lifetime of the model between the company’s updated revised base case and the ERG’s revised analysis (approximately £74,500 per QALY gained).</td>
</tr>
<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>The committee considered that the most plausible ICER was approximately £74,500 per QALY gained.</td>
</tr>
<tr>
<td>Additional factors taken into account (TA309)</td>
<td>-</td>
</tr>
</tbody>
</table>

Patient access schemes (PPRS) | Not applicable. | - |
The committee considered that pemetrexed did meet NICE's supplementary advice on end of life treatments. It noted that even taking into account supplementary advice on end-of-life treatments, the most plausible ICER was higher than that normally considered to be cost effective.

The committee did not identify any special factors that would require or justify making a positive recommendation despite the very high ICER.

Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after pemetrexed and cisplatin subject to the conditions in section 1.1. The committee agreed that population covered by the commercial access agreement (people whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and whose Eastern Cooperative Oncology Group [ECOG] performance status was 0 or 1 at the start of maintenance treatment) was in line with both PARAMOUNT and clinical practice.

Given the new cost-effectiveness analysis, including the commercial access agreement, and considering the end-of-life criteria were met, the committee recommended pemetrexed maintenance treatment after pemetrexed and cisplatin as a cost-effective use of NHS resources.

The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

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 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.

5.4 NHS England and Eli Lilly and Company have agreed a commercial access agreement that makes pemetrexed for continuation maintenance treatment (that is, after pemetrexed and cisplatin induction therapy) available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to productsupply@lilly.com.
6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

NICE project team

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

TA309

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Cancer Drugs Fund reconsideration of TA309

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Accreditation

NICE accredited
www.nice.org.uk/accreditation