

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final Appraisal Determination

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

This guidance was developed using the single technology appraisal (STA) process.

## **1 Guidance**

- 1.1 Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer.
- 1.2 People currently receiving pemetrexed should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

## **2 The technology**

- 2.1 Pemetrexed (Alimta, Eli Lilly and Company) is an antifolate agent that works by disrupting folate-dependent metabolic processes essential for cancer cell replication and survival. It is licensed as a monotherapy for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy. For further information see the summary of product characteristics (SPC).
- 2.2 Pemetrexed is associated with suppression of bone marrow function, nausea and vomiting, fatigue and a range of other side effects. For full details of side effects and contraindications, see the SPC.

- 2.3 The recommended dose of pemetrexed is 500mg/m<sup>2</sup> body surface area (BSA). It is administered by intravenous infusion over 10 minutes on the first day of each 21-day cycle.
- 2.4 The acquisition cost of pemetrexed is £800 for a 500-mg vial (excluding VAT; 'British national formulary' [BNF], 52nd edition). Costs may vary in different settings because of negotiated procurement discounts.

### **3 The manufacturer's submission**

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of pemetrexed and a review of this submission by the Evidence Review Group (ERG; appendix B). The Institute and the ERG sought clarification on aspects of the manufacturer submission.

- 3.1 The manufacturer approached the decision problem by comparing pemetrexed with docetaxel and with best supportive care (BSC). The population under consideration had locally advanced or metastatic NSCLC and had relapsed after previous chemotherapy. The primary outcome measure outlined in the decision problem was overall survival. Secondary outcome measures included time to documented progression of disease, progression-free survival, duration of tumour response, quality of life and the incidence of adverse events.
- 3.2 The manufacturer's submission presented evidence on the clinical effectiveness of pemetrexed from one open-label randomised controlled trial (RCT) that compared pemetrexed with docetaxel (the JMEI trial). Final analysis showed no significant difference in median overall survival; 8.3 months with pemetrexed versus 7.9 months with docetaxel ( $p = 0.93$  for ITT superiority). The hazard ratio [HR] was 0.99 (95% confidence interval [CI], 0.82 to 1.20) with a non-inferiority  $p$ -value of 0.226 for testing HR of  $<1.11$ . This

means that the non-inferiority criteria were not met using the fixed margin method. Prior to un-blinding of the trial data, another (secondary) non-inferiority criterion was defined in the analysis plan, whereby non-inferiority was defined by HR <1.21. This 'percentage efficacy method' was used to determine whether pemetrexed retained at least 50% of the assumed efficacy of docetaxel over BSC, using docetaxel efficacy data from an RCT of docetaxel compared with BSC (HR 0.56; 95% CI, 0.35 to 0.88). The estimate of the percentage of survival benefit (docetaxel over BSC) retained by pemetrexed was 102% (95% CI, 52% to 157%) with a non-inferiority p-value of 0.047 for testing 50% retention.

- 3.3 Regarding adverse effects reported in the RCT, compared with docetaxel, pemetrexed was associated with fewer grade 3 and 4 haematological toxicities; less neutropenia ( $p < 0.001$ ), febrile neutropenia ( $p < 0.001$ ) and neutropenia with infection ( $p = 0.004$ ). There were fewer hospitalisations for neutropenic fever ( $n = 4$  for pemetrexed and  $n = 35$  for docetaxel) ( $p < 0.001$ ) and reduced use of granulocyte colony-stimulating factor (G-CSF;  $n = 7$  for pemetrexed versus  $n = 53$  for docetaxel  $p < 0.001$ ) in the pemetrexed group. No differences between the groups were found for anaemia (or number of patients receiving red blood cell transfusions or erythropoietin) or thrombocytopenia. There were also no differences for 10 of the 12 non-haematological toxicities reported, but the docetaxel group had more alopecia ( $p < 0.001$ ) and a higher percentage of the pemetrexed group had raised levels of alanine transferase, an indicator of impaired liver function ( $p = 0.028$ ). No statistically significant differences were reported for rate of hospitalisations for any other drug-related adverse event.
- 3.4 The RCT reported no differences between treatments in disease-specific quality of life, measured using the Lung Cancer Symptom Scale, which includes six symptoms (anorexia, fatigue, cough, dyspnoea, haemoptysis and pain).

- 3.5 The manufacturer's submission presented an economic analysis based on a Markov model with a 3-year time horizon. The estimates of efficacy used in the economic model were based on an unadjusted indirect comparison of absolute overall survival in which weighted estimates of absolute survival were pooled from single arms of different trials in published literature. The median absolute overall survival was estimated to be 8.3 months for pemetrexed (95% CI, 6.9 to 9.7) based on the results of the JME1 trial, 7.0 months for docetaxel (95% CI, 5.6 to 9.9) based on the pooled results of seven trials, and 4.9 months for BSC (95% CI, 4.2 to 5.5) based on the pooled results of three trials. When these absolute overall survival parameters were put into the economic model, the predicted mean life years gained were estimated to be 11.0 months for pemetrexed, 8.8 months for docetaxel and 7.2 months for BSC. The manufacturer's base-case analysis resulted in an incremental cost-effectiveness ratio (ICER) of £18,672 per additional quality-adjusted life year (QALY) gained for pemetrexed compared with docetaxel and an ICER of £16,458 per additional QALY gained for pemetrexed compared with BSC.
- 3.6 An adjusted indirect comparison, conducted as a sensitivity analysis, pooled median overall survival from single arms of the trials to estimate hazard rates for each treatment group. The adjusted indirect comparison estimated the life years gained to be 14.4 months for pemetrexed and 12.4 months for docetaxel. This analysis found that the mean ICER of pemetrexed compared with docetaxel was £31,612 per additional QALY gained and the mean ICER of pemetrexed compared with BSC was £10,298 per additional QALY gained.
- 3.7 The ERG reviewed the evidence submitted for clinical and cost effectiveness. The ERG judged that the open-label RCT had not proved formally the equivalent efficacy of pemetrexed compared to docetaxel, and had not demonstrated that pemetrexed was more

efficacious than docetaxel. The ERG's viewpoint on the manufacturer's use of an indirect comparison to generate estimates of efficacy for its model, was that that indirect comparison is only acceptable where direct comparison evidence is not available. The ERG noted that the manufacturer's indirect comparison estimate of mean survival with docetaxel was less than the survival estimate obtained from the head-to-head trial (7.14 compared with 8.74 months, respectively). The ERG considered that the use of an unadjusted indirect comparison for the base case was not ideal because it was based on pooling of median absolute survival estimates from individual arms of the trials rather than a consideration of the relative treatment effects. The ERG also noted that the estimates of drug acquisition costs used needed adjustment; in particular, the number of chemotherapy cycles should have reflected the number of cycles reported in the head-to-head trial.

3.8 The ERG considered the effect on the ICER of assuming equivalent overall survival for pemetrexed and docetaxel, in place of the manufacturer's assumption of greater survival. In this situation, the ERG estimated that the ICER for pemetrexed versus docetaxel would increase to approximately £458,000 per additional QALY gained. It also noted that if the revised estimates of drug acquisition/administration costs, costs of treating adverse events, and non-treatment-related and palliative care costs were included in the analysis, the ICER for pemetrexed versus docetaxel could be up to £1.8 million per additional QALY gained.

3.9 The ERG evaluated the manufacturer's economic analysis of pemetrexed versus BSC. Based on the manufacturer's estimates of survival and QALYs for the BSC group, but using a survival effect of pemetrexed equivalent to docetaxel, and revised cost estimates, the ERG estimated an ICER of approximately £60,000 per additional QALY gained.

## **4 Consideration of the evidence**

4.1 The Appraisal Committee (appendix A) reviewed the data available on the clinical and cost effectiveness of pemetrexed for the treatment of NSCLC, having considered evidence (appendix B) on the nature of the condition and the value placed on the benefits of pemetrexed by people with NSCLC, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources

### **Pemetrexed compared with docetaxel**

4.2 The Committee considered the evidence on the clinical effectiveness of pemetrexed for the treatment of NSCLC. It considered the data presented by the manufacturer that compared pemetrexed with docetaxel, and concluded that overall survival with pemetrexed was not significantly greater than with docetaxel, and that the results of non-inferiority testing did not formally exclude the possibility of a marginal loss of efficacy of pemetrexed when compared with docetaxel.

4.3 The Committee heard from the clinical specialists and patient experts that pemetrexed was a potential treatment for relapsed patients with NSCLC, for whom there are few treatment options. The Committee also heard that some patients may prefer pemetrexed to docetaxel because of its different side-effect profile, particularly the lower rate of alopecia. However, the clinical specialists considered that patients undergoing second-line chemotherapy treatment usually valued other effects of treatment more highly, in particular increased life expectancy and overall quality of life. The Committee acknowledged that hair loss can be distressing, but concluded that a higher rate of alopecia would not normally preclude consideration of a particular chemotherapy regimen. It concluded that the reduction in rates of alopecia was

not sufficient reason to recommend pemetrexed as an alternative to docetaxel.

- 4.4 The Committee considered the manufacturer's assessment of the cost effectiveness of pemetrexed compared with docetaxel. It discussed both the base-case analysis based on an unadjusted indirect comparison of pooled absolute survival estimates from several trials, and a sensitivity analysis based on an adjusted indirect comparison of pooled rates from several trials. It considered both indirect comparisons inappropriate given the inconsistency of the findings in relation to the direct randomised comparison between pemetrexed and docetaxel in the JME1 trial. The Committee noted that both the base-case analysis (which estimated a mean survival of 11.0 months for pemetrexed and 8.8 months for docetaxel) and the adjusted indirect comparison (mean survival of 14.4 months for pemetrexed and 12.4 months for docetaxel) both contradicted the results of the RCT, which showed that the mean survival was 8.56 months for pemetrexed and 8.74 months for docetaxel. The Committee concluded that the survival estimates included in the manufacturer's economic analysis were inappropriate.
- 4.5 The Committee considered the ERG's review of the economic analysis. The Committee noted that if an assumption of equivalent survival for docetaxel and pemetrexed was used in the economic analysis, the resulting ICER for pemetrexed compared with docetaxel would be over £450,000 per additional QALY gained.
- 4.6 The Committee also considered the estimates of cost included in the manufacturer's economic analysis, particularly those relating to the number of cycles of treatment and the inclusion of non-treatment costs (including BSC). The Committee concluded that the estimate of clinical effectiveness and of the number of treatment cycles should be based on the same source – that is, the

registration trial in which a mean of 4.4 cycles was used. It noted that even if, in clinical practice, the number of cycles used is lower than this, the clinical effectiveness of shorter regimens (for example, the three cycles of treatment which were included in the manufacturer's analysis) was unknown. The Committee also considered the appropriateness of the estimates of patient average BSA. The Committee acknowledged that BSA would vary between patients and concluded that the mean BSA could be lower than the ERG estimate, particularly in patients with relapsed NSCLC. The Committee considered the manufacturer's estimate to be appropriate, but concluded that this factor would not substantially change the ICER. The Committee noted that if the ERG's revised estimates of costs were included, the ICER for pemetrexed compared with docetaxel would be greater than £1 million per additional QALY gained.

- 4.7 The Committee considered whether the cost of G-CSF or the treatment of neutropenia had been adequately taken into account by the manufacturer. The Committee noted that the cost of G-CSF was not explicitly included in the ERG review of the manufacturer's economic evaluation. However, the ERG highlighted that the costs of some G-CSF usage would be included in its cost estimates which were based on NHS reference costs. The Committee acknowledged there was uncertainty about the extent of G-CSF usage in clinical practice in the UK, and considered that if G-CSF were used to the extent suggested by the experts, inclusion of this factor would not lead to a substantial improvement in the cost effectiveness of pemetrexed compared with docetaxel.

#### **Pemetrexed compared with best supportive care**

- 4.8 The Committee also considered the use of pemetrexed in people who had previously received docetaxel or for whom docetaxel therapy was unsuitable. The Committee heard from the clinical specialists that some patients experience mild allergic reactions to



docetaxel (such as rash or nausea). In these circumstances it is usual to treat the reaction rather than discontinue treatment. The Committee also heard that some patients experience a severe neuropathic reaction to first-line platinum-based chemotherapy or an anaphylactic reaction (such as bronchospasm or hypotension) to docetaxel, and that initiation or continuation of docetaxel second-line therapy might therefore be unsuitable for them. However the Committee noted that these types of toxicity and allergic reactions are rare.

- 4.9 The Committee heard that the RCT of pemetrexed did not include patients who could not receive docetaxel and it was therefore concerned that the clinical effectiveness of pemetrexed had not been established in this context. Nevertheless, the Committee considered the calculations on the cost effectiveness of pemetrexed compared with BSC. It noted that the manufacturer's analysis assumed that mean survival for patients receiving pemetrexed was 11.0 months but considered that the mean survival from the RCT of pemetrexed (8.56 months) was more credible.
- 4.10 The Committee noted that if the ERG's revised estimates of costs were used in the analysis, the ICER would be over £40,000 per additional QALY gained. It also noted that if the ERG's revised estimates of effectiveness were also included the ICER would be nearly £60,000 per additional QALY gained.
- 4.11 The Committee also considered the appropriateness of the cost estimates of BSC or non-treatment-related costs required in the two treatment arms. It noted that the manufacturer's cost estimates assumed that those receiving pemetrexed would only require treatment for adverse effects of treatment and not for disease-related symptoms (supportive care). The ERG suggested that the costs of treating disease-related symptoms would be the same for

both treatment arms. The Committee proposed that those treated with pemetrexed would receive some underlying supportive care, but that this was plausibly at a lower rate than for patients not receiving active treatment. The Committee considered that if the cost of underlying supportive care for people receiving active treatment was 50% of that for people who were not, and using the ERG's other cost and survival assumptions (including the manufacturer's pooled estimate of mean overall survival for BSC of 7.2 months), the incremental cost would be approximately £8,000, resulting in an ICER of over £50,000 per additional QALY gained.

### **Summary**

- 4.12 The Committee concluded that pemetrexed would not be a cost-effective use of NHS resources when compared with either docetaxel or BSC. After considering all the evidence available, the Committee concluded that pemetrexed could not be recommended for the treatment of locally advanced or metastatic NSCLC.

## **5 Implementation**

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals, normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external

review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TAXXX](http://www.nice.org.uk/TAXXX)). [Note: tools will be available when the final guidance is issued]

## **6 Related NICE guidance**

- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 24 (2005). Available from: [www.nice.org.uk/CG024](http://www.nice.org.uk/CG024)

- 6.1 NICE is developing the following guidance (see [www.nice.org.uk](http://www.nice.org.uk) for details).

- Erlotinib for the treatment of non-small-cell lung cancer. (publication expected March 2007)
- Pemetrexed disodium for the treatment of mesothelioma (publication expected September 2007).

## **7 Review of guidance**

- 7.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

7.2 The guidance on this technology will be considered for review in January 2010.

Andrew Stevens  
Chair, Appraisal Committee  
January 2007

## **Appendix A. Appraisal Committee members and NICE project team**

### **A. 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 the chair and a vice chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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

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

#### **Professor David Barnett**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr David W Black**

Director of Public Health, Chesterfield PCT

#### **Mr Brian Buckley**

Chairman, Incontact

#### **Professor Mike Campbell**

Professor of Medical Statistics, University of Sheffield

#### **Dr Carol Campbell**

Senior Lecturer, University of Teesside

**Dr Peter Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology,  
Merseyside

**Ms Jude Cohen**

Manager of Resources & Administration, Council for Psychotherapy (UKCP)

**Dr Christine Davey**

Senior Researcher, North Yorkshire Alliance R&D Unit

**Dr Mike Davies**

Consultant Physician, Manchester Royal Infirmary

**Mr Richard Devereaux-Phillips**

Public Affairs Manager, Medtronic Ltd

**Dr Rachel A Elliott**

Clinical Senior Lecturer, The University of Manchester

**Mrs Eleanor Grey**

Lay Member

**Dr Dyfrig Hughes**

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of  
Health and Policy in Health, University of Wales, Bangor

**Dr Catherine Jackson**

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

**Dr Peter Jackson**

Clinical Pharmacologist, the University of Sheffield

**Professor Peter Jones**

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

**Ms Rachel Lewis**

Nurse Advisor to the Department of Health

**Dr Damien Longson**

Consultant in Liaison Psychiatry, North Manchester General Hospital

**Professor Jonathan Michaels**

Professor of Vascular Surgery, University of Sheffield

**Dr Eugene Milne**

Deputy Medical Director, North East Strategic Health Authority

**Dr Simon Mitchell**

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

**Dr Martin J Price**

Head of Outcomes Research, Janssen-Cilag Ltd

**Mr Miles Scott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Professor Mark Sculpher**

Professor of Health Economics, University of York

**Professor Andrew Stevens**

Chair of Appraisal Committee C

**Dr Cathryn Patricia Thomas**

Senior Lecturer, Department of Primary Care & General Practice

## **B. NICE project team**

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

### **Helen Tucker**

Technical Lead

### **Louise Longworth**

Technical Adviser

### **Chris Feinmann**

Project Manager



## Appendix B. Sources of evidence considered by the Committee

- A The following manufacturer/sponsor provided a submission for this appraisal:
- Eli Lilly and Company Ltd.
- B The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):
- Bagust A, Boland A, Dundar Y, Davis H, Dickson R, Green J, Hockenhill J, Macbeth F, McLeod C, Proudlove C, Stevenson J, Walley T. (September 2006) Pemetrexed for the treatment of relapsed non-small cell lung cancer
- C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They gave their expert personal view on pemetrexed by providing written and oral evidence to the Committee. They were also invited to comment on the appraisal consultation document (ACD).
- Dr Jesme Baird, Director of Patient Care, nominated by the Roy Castle Lung Cancer Foundation as a patient expert
  - Professor David R Ferry, Medical Oncologist, New Cross Hospital, Wolverhampton, nominated by the Royal College of Physicians
  - Dr Mary O'Brien, Consultant Medical Oncologist, Institute of Cancer Research, nominated by the Institute of Cancer Research
  - Dr Elizabeth Sawicka, Consultant, Princess Royal University Hospital, nominated by The British Thoracic Society

## **Appendix C. List of organisations involved in this appraisal**

The following organisations accepted the invitation to participate in this appraisal. They were also invited to comment on the ACD and supporting evidence. Consultee organisations have the opportunity to appeal against the final appraisal determination (FAD):

### **I Professional/specialist and patient/carer groups:**

- British Thoracic Oncology Group
- British Thoracic Society
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- CancerBackup
- Department of Health
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Tenovus Cancer Information Centre
- Welsh Assembly Government

### **II Commentator organisations (without the right of appeal):**

- British National Formulary
- British Thoracic Oncology Group
- MRC CTU - Lung Cancer and Mesothelioma Group
- National Collaborating Centre for Cancer
- NHS Quality Improvement Scotland
- Roche Products Ltd.
- Sanofi-Aventis