NICE National Institute for Health and Care Excellence

NICE guidance

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

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 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

1.1 Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer after chemotherapy.

1.2 People currently receiving pemetrexed should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Information about pemetrexed

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^2 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; BNF, edition 52). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The manufacturer's submission

The appraisal committee considered evidence submitted by the manufacturer of pemetrexed and a review of this submission by the evidence review group (ERG). NICE 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 1 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 less than 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 of less than 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 6 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 JMEI trial, 7.0 months for docetaxel (95% CI, 5.6 to 9.9) based on the pooled results of 7 trials, and 4.9 months for BSC (95% CI, 4.2 to 5.5) based on the pooled results of 3 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 when 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 or 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.

Consideration of the evidence

3.10 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pemetrexed for the treatment of NSCLC, having considered evidence 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

3.11 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.

3.12 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.

3.13 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 JMEI 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.

3.14 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.

3.15 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 3 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.

3.16 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 was 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

3.17 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.

3.18 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.

3.19 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.

3.20 The Committee also considered the appropriateness of the cost estimates of BSC or non-treatment-related costs required in the 2 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

3.21 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.

4 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committee is a standing advisory committee of NICE. 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 3 times a month except in December, when there are no meetings. The Committee membership is split into 3 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 Teeside

Dr Peter Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Ms Jude Cohen
Manager of Resources and Administration, Council for Psychotherapy (UKCP)

Dr Christine Davey
Senior Researcher, North Yorkshire Alliance R and 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, 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, University of Sheffield

Professor Peter Jones
Professor of Statistics and 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 and General Practice

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), a technical adviser and a project manager.

Helen Tucker
Technical Lead

Louise Longworth
Technical Adviser

Chris Feinmann
Project Manager

Sources of evidence considered by the Committee

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

- Bagust A et al Pemetrexed for the treatment of relapsed non-small cell lung cancer, September 2006.

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope. Companies or sponsors were also invited to make written submissions. Professional or specialist, and patient or carer groups, gave their expert views on pemetrexed by providing a written statement to the Committee. Companies or sponsors, and professional or specialist, and patient or carer groups, have the opportunity to appeal against the final appraisal determination.

Company or sponsor:

- Eli Lilly and Company Ltd.

Professional or specialist, and patient or 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

Commentator organisations (did not provide written evidence and 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

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on pemetrexed by providing oral evidence to the Committee.

- Dr Jesme Baird, Director of Patient Care, nominated by the Roy Castle Lung Cancer Foundation – patient expert
- Professor David R Ferry, Medical Oncologist, New Cross Hospital, Wolverhampton, nominated by the Royal College of Physicians – clinical specialist
- Dr Mary O'Brien, Consultant Medical Oncologist, Institute of Cancer Research, nominated by the Institute of Cancer Research – clinical specialist
- Dr Elizabeth Sawicka, Consultant, Princess Royal University Hospital, nominated by The British Thoracic Society – clinical specialist

Update information

February 2019: Recommendation wording amended for clarity about the use of pemetrexed.

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