NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of Technology Appraisal TA124: Pemetrexed for the treatment of non-small-cell lung cancer

This guidance was issued in August 2007 with a review date of January 2010. This review date has been brought forward in order to take account of a recent change in license.

Recommendation

- The guidance should be transferred to the 'static guidance list'. That we consult on the proposal.

Consideration of options for recommendation:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	It is noted that the part of licence that is relevant to TA124 has been restricted, following an unplanned retrospective analysis of pre-existing data, however we do not feel that this is significant enough to warrant an appraisal.
The decision to review the guidance should be deferred.	The present case for a review is entirely based on a retrospective sub-group analysis of the existing data, which only just reaches statistical significance for overall survival. One relevant phase III RCT has been completed since the original review, but this has yet to be published. However, this trial does not have pre-planned subgroups likely to result in data useful to settle the issue of efficacy in the licensed subgroup. We propose that this appraisal should be added to the static list, however we note that further trials involving pemetrexed have been planned. If these generate significant findings the decision to review would be revisited in due course.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review	It is not clear that a review is necessary at present, so this may be considered a poor use of NICE resources.

of the related technology.	
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	It is not clear that a review is necessary, so this may be considered a poor use of NICE resources.
A review of the guidance should be incorporated into an on-going clinical guideline.	A review of the current NICE lung cancer clinical guideline is due in March 2011. Chemotherapy for NSCLC has been excluded from the remit of this guideline following a post-scoping amendment. The CG will indicate how NSCLC will be approached. We propose to defer to this guidance on whether, if at all, a review of TA124 should be incorporated into a CG.
A review of the guidance should be transferred to the 'static guidance list'.	Although we recognise that the license indications for pemetrexed have been restricted, the estimates of cost-effectiveness are unlikely to change to the degree required to result in a change of the recommendations. We therefore recommend this guidance should be transferred to the static list.

Original remit(s)

To appraise the clinical and cost effectiveness of pemetrexed (within the context of the licensed indication) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Current 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.

Relevant Institute work

Published:

Lung cancer: the diagnosis and treatment of lung cancer. Clinical guideline 24 (2005).

Erlotinib for the treatment of non-small-cell lung cancer. Technology appraisal 162 (2008).

In progress:

The diagnosis and treatment of lung cancer (update). Clinical guideline (publication expected March 2011).

Pemetrexed for the first line treatment of non-small-cell lung cancer. Technology appraisal (publication expected September 2009).

Pemetrexed for the maintenance treatment of non-small-cell lung cancer. Technology appraisal (publication expected May 2010).

Cetuximab for the treatment of advanced non-small-cell lung cancer. Technology appraisal (publication date TBC).

Erlotinib (in combination with bevacizumab) for the maintenance treatment of advanced or metastatic non-small-cell lung cancer. Technology appraisal (publication expected October 2010).

Erlotinib (in combination with bevacizumab) for the second-line treatment of advanced or metastatic non-small-cell lung cancer. Technology appraisal (publication expected October 2010).

Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer after previous platinum-containing chemotherapy. Technology appraisal (publication expected August 2010).

Vandetanib for the second and subsequent line treatment of non-small-cell lung cancer after previous platinum containing chemotherapy. Technology appraisal (publication expected November 2010).

Terminated:

Bevacizumab for the treatment of non-small-cell lung cancer. Terminated technology appraisal 148 (2008).

Gefitinib for the second-line treatment of non-small-cell lung cancer. Technology appraisal suspended May 2009.

Safety information

In their June 2008 newsletter, the Food and Drug Administration (FDA) gave information on "reports of radiation recall associated with pemetrexed (marketed as Alimta®). Radiation recall is an inflammatory reaction limited to previously irradiated areas of the body that occurs following the subsequent administration of a drug."

Details of new indications

Drug (manufacturer)	Details
Pemetrexed (Eli Lilly)	Current SPC states that pemetrexed is indicated: *"as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology".* This is the indication covered by TA124. Note that the underlined phrase, which has narrowed the licensed indication, has been added since the publication of TA124 following an unplanned sub-group analysis of the data used in TA124. Pemetrexed is also licensed: "*in combination with cisplatin ... for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology"*. This aspect of the licence is covered by an upcoming NICE Technology Appraisal. A further (potential) extension, which will cover use as maintenance therapy, is also already covered on the NICE work programme.

Details of new products

Aflibercept (Sanofi-Aventis)	Phase III in combination with docetaxel as second line therapy for NSCLC

BIBF 1120 (Boehringer Ingelheim)	Phase III combined with pemetrexed as second line therapy for NSCLC
Vandetanib (AstraZeneca)	Phase III combined with pemetrexed as second line therapy for NSCLC
Talactoferrin alfa (Agennix)	Phase III as monotherapy (2nd line) for NSCLC
Vadimezan (Novartis)	Phase III in combination with docetaxel as second line therapy for NSCLC
Erlotinib (Roche)	Covered in TA162, issued November 2008.
Bevacizumab (AstraZeneca)	Licensed but not recommended by NICE: guidance was suspended as no submission was received. Phase III trial in combination with erlotinib as second line therapy for NSCLC failed to show advantage in terms of overall survival.
Gefitinib	Licensed. Guidance suspended as no manufacturer submission was received.

On-going trials

Title	Details
Pemetrexed or Erlotinib as Second-Line Therapy in Treating Patients With Advanced Non-Small Cell Lung Cancer	Phase III Estimated primary completion date: May 2011 Currently recruiting
Trial of Pemetrexed Versus Erlotinib in Pretreated Patients With Non Small Cell Lung Cancer (NSCLC)	Phase III Estimated primary completion date: May 2011 Currently recruiting
Pharmaco-Economic Study of a Second Line Treatment in Advanced Non Small Cell Lung Cancer	Phase III Estimated primary completion date: not stated Currently recruiting
Chemotherapy for Patients With Non-Small Cell Lung Cancer	Phase IV (single arm) Estimated primary completion date: April 2009

	Ongoing
A Study of Tarceva (Erlotinib) and Standard of Care Chemotherapy in Patients With Advanced, Recurrent, or Metastatic Non-Small Cell Lung Cancer (NSCLC)	Phase III Erlotinib vs. Pemetrexed vs. Docetaxel Estimated completion date: August 2014 Currently recruiting
Chemotherapy for Patients With Non-Small Cell Lung Cancer	Phase III Pemetrexed vs. Docetaxel (2nd line) Completed December 2008
A Comparison of Two Doses of Pemetrexed in Patients Who Have Lung Cancer	Phase III Completed April 2008

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from January 2006 onwards were reviewed.

Implementation

A submission from Implementation is attached at the end of this paper.

Equality and diversity issues

None identified.

Appraisals comment

The MA for second-line pemetrexed in locally advanced or metastatic NSCLS has been updated to exclude tumours with predominantly squamous cell histology based on a post-hoc subgroup analysis.

The change to the indication occurred as a result of the application to extend the indication to include first line treatment of locally advanced or metastatic NSCLC. This indication was supported by a non-inferiority trial comparing pemetrexed plus cisplatin with gemcitabine plus cisplatin. Overall this study demonstrated non-inferiority of pemetrexed plus cisplatin as compared to gemcitabine plus cisplatin in terms of overall survival, but the prospectively planned sub-group analyses of treatment effect by histology revealed a strong

signal. This indicated lower efficacy of pemetrexed versus gemcitabine (in the context of the combination treatment) in the histological sub-group squamous cell carcinoma. Therefore, the CHMP concluded that the benefit/risk ratio of pemetrexed/cisplatin in squamous cell NSCLC was clearly negative since gemcitabine/cisplatin offered prolonged survival compared to pemetrexed/cisplatin. However, the benefit/risk ratio in the remainder NSCLC population without predominantly squamous cell histology (that is, adenocarcinoma or large cell NSCLC) was clearly positive, where pemetrexed/cisplatin offered prolonged survival compared to gemcitabine/cisplatin.

Retrospective sub-group analyses of two preceding trials investigating pemetrexed as monotherapy in second line treatment of NSCLC also indicated lower efficacy of pemetrexed in the histological sub-group squamous cell carcinoma. Consequently the existing second- line monotherapy indication was amended.

Subgroups by histological type were not considered in the economic analysis for the original TA124 appraisal and the ICERs for the entire trial population were £1,000,000/QALY (compared to docetaxel) and >£50,000/QALY (compared with BSC). It would be expected that restricting the indication to adenocarcinoma or large cell NSCLC would result in lower ICERs because the estimate of effectiveness would be greater than for the overall group. About 40-45% of NSCLC is adenocarcinoma, while large cell carcinoma accounts for less than <10%. However, given that these estimates would be based on post-hoc subgroup analysis, they would be less reliable than estimates based on an overall study result and therefore associated with additional uncertainty. A further ongoing trial (primary outcome data available Dec 2008) has been identified but does not prospectively identify any subgroups.

Pemetrexed is currently being appraised for the first-line treatment (expected Sept 2009) and maintenance treatment (expected May 2010) of NSCLC. Positive recommendations in these indications will reduce the use of pemetrexed at subsequent lines. In addition, erlotinib is recommended at second-line (TA 162) and there are planned appraisals of other agents [topotecan (expected Nov 2009) and vandetanib (expected Nov 2010]. Positive recommendations for these agents will decrease interest in the use of pemetrexed at second-line. The lung cancer: diagnosis and treatment, clinical guideline (CG24) is currently being updated (expected March 2011). Chemotherapy for NSCLC has been excluded from this guideline following a post-scoping amendment. However the guideline will give some indication of how this exclusion for NSCLC will be addressed, possibly as a short clinical guideline taking in to account all guidance for the topic current at the time.

An update of the appraisal, where the drug was not more efficacious and the estimates of cost-effectiveness were unpromising, in the absence of good quality evidence for the subgroup in the updated marketing authorisation, would not be a good use of resources, It would seem reasonable to defer the review of this guidance to July 2011, when the decision on the possible guideline for chemotherapy for NSCLC would be made and the availability of any evidence to support a review of the amended MA can be assessed.

Commercial in confidence information has been removed

Summary

Despite the modified marketing authorisation, there is unlikely to be good quality data to evaluate the cost-effectiveness of pemetrexed for the newly licensed population. The estimates of cost-effectiveness are unlikely to change to the degree required to result in a change of the recommendations. The best use of resources would be for the guidance to become static. Topics on the static list may be transferred back to the active list for further appraisal if new evidence becomes available that is likely to have a material effect on the last guidance issued. At a later stage consideration can be given to updating it within the context of a NSCLC chemotherapy clinical guideline (if such a guideline is planned) and the evidence for the amended MA can be assessed.

GE paper sign off:

Nina Pinwill, Associate Director, CHTE, NICE
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Contributors to this paper:

Information Specialist: Toni Price
Information Specialist: Tom Hudson
Technical Lead: Elangovan Gajraj
Technical Adviser: Janet Robertson
Implementation Analyst: Mariam Bibi
Project Manager: Natalie Bemrose

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

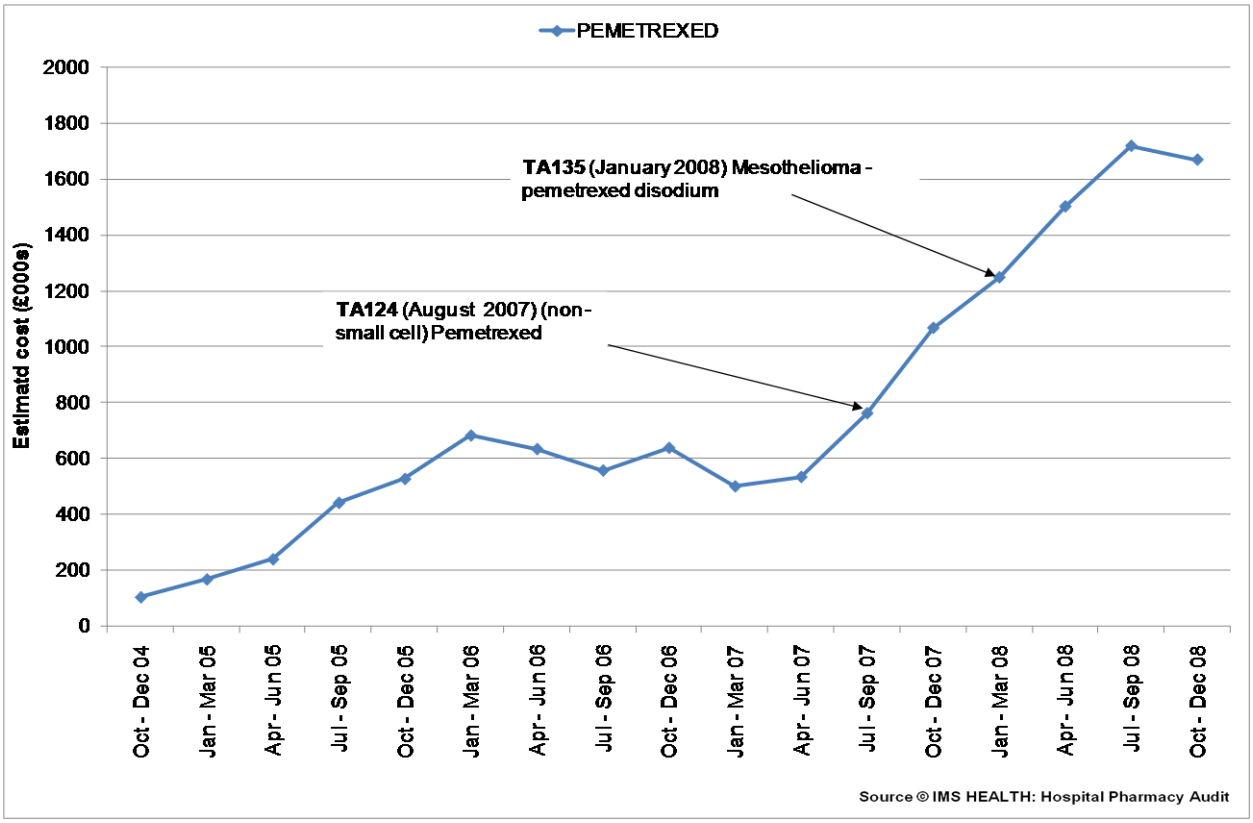
IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 124: Guidance on pemetrexed for the treatment of lung cancer (non-small cell).

1. National Hospital Prescribing Data

Data showing trends in prescribing costs are presented below. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.



2. External literature

2.1 The Information Centre for Health and Social Care (2008) Hospital Prescribing, 2007: England

http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/hospital-prescribing-2007:-england

Data showing the use of pemetrexed.

Cost (£000s)	Primary care	% growth primary	FP10HP*	% growth	Hospital	% growth hospital	Total	% growth total
Pemetrexed	**0.0**	**-**	**0.0**	**-**	**2,870.1**	**14.4**	**2,870.1**	**14.4**

*FP10HP = prescriptions written in hospitals but dispensed in the community

The data shows that all prescribing for pemetrexed is carried out in a hospital setting. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.