NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Pemetrexed disodium for the treatment of mesothelioma

Response to consultee and commentator comments on the draft scope

Consultee	Subject in Scope	Comment	Response
Eli Lilly	Objectives	the treatment of **unresectable** malignant pleural mesothelioma **in chemo-naïve patients**	Words in bold added
Eli Lilly	Background	This system has been superseded by the TNM system proposed by the International Mesothelioma Interest Group (Pistolesi et al, 2004).	
Cancer BACUP	Background	We would recommend that the word 'poudrage' (paragraph 1, page 2) should be removed and the phrase replaced with 'talc pleuradhesis (drainage of fluid from the pleural cavity followed by the insertion of talc to prevent further fluid accumulation)'. Pleuradhesis is a commonly used word in medicine and would avoid confusion.	Changed as suggested
HSE	Background	Over 99% of deaths caused by mesothelioma have been linked to asbestos exposure. When asbestos fibres are inhaled or swallowed, they **may** cause scarring of the lung tissues, **cancer of the bronchial tree ("lung cancer")** and sometimes cancers in the pleura and peritoneum. Cases of mesothelioma occur in people who have worked in a **wide range of occupations, notably shipbuilding, railway engineering, and asbestos product manufacture**. **Those involved in building demolition, maintenance and repair are also particularly at risk.** Family members of people	All changes in bold were added as suggested.

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		whose work clothes were contaminated have also developed mesothelioma. The use of all asbestos was banned in 1999 in the UK. Mesothelioma does not usually develop until 10-60 years after exposure to asbestos, the median time being of the order of 40 years. Currently, about **1850** people in the UK are diagnosed with mesothelioma each year. It is estimated that the number of people diagnosed with mesothelioma each year will increase to a peak of over 2000 cases each year between years **2011 and 2015**, reflecting a lag from the highest use of asbestos in the 1970s. **An estimated 65,000 cases are expected to occur between 2002 and 2050.**	
LRiG	Intervention	We suggest the intervention section should be amended to "Pemetrexed disodium and cisplatin in combination supplemented with folic acid and vitamin B_{12}". This is in line with the recommendations made by the European Medicines Agency (EMEA).[1]	Intervention section not altered. The point being made has been put into other considerations.
Eli Lilly	Comparators	(in part, as some confidential data included)…. best supportive care and chemotherapy only are the most common approaches used to treat mesothelioma. Vinorelbine, pemetrexed only and pemetrexed/cisplatin were the three most common chemotherapy regimens used.	Used to inform the comparators section

[1] European Medicines Agency- Summary of product characteristics (Annex I). http://www.emea.eu.int/humandocs/PDFs/EPAR/alimta/H-564-PI-en.pdf

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Cancer BACUP	Comparators	There are many different chemotherapy agents which have been used for mesothelioma with varying but generally poor success. Antifolates such as methotrexate have shown some benefit. The chemotherapy regimens currently being used in the open MS01 trial are MVP (mitomycin C, vinblastine and cisplatin) and vinorelbine.	Changed
MRC trials unit	Comparators	Our understanding is that a variety of chemotherapy regimens are used in the UK, and there is little consensus on a standard treatment. Within the MS01 randomised trial we are using MVP (mitomycin, vinblastine and cisplatin) and single-agent navelbine, as both these regimens have been shown in phase II studies to give good symptom palliation. However, importantly, cisplatin alone is not a recognised regimen for this disease.	Add navelbine to comparators; other comparators already included from other comments
LRig	Outcomes	1 We feel there would be value in exploring 'time to abandoning treatment' and suggest that outcome measures to be considered in the review should include this outcome. 2 We also feel that the outcome measures including performance status, tumour response and progression free survival are unlikely to provide useful or relevant data in this particular disease in relation to this review and suggest that they are not to be considered in the review.	
Eli Lilly	Other considerations	1 The most basic grouping is by disease extent; advanced (Stage III/IV) and inoperable, or localised (Stage I/II) and, barring other co-morbidities, therefore operable. 2 There are no formal stopping criteria with pemetrexed and as with any palliative treatment, the decision to stop is based upon	1 Staging defines the appraisal (patients must be resectable) and is not therefore very useful for subgroup analysis 2 Used to inform other

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		continuing patient benefit. This is a discussion that should take place between the treating physician, the patient, and their carers	considerations
Cancer BACUP	Other considerations	1 To date, no identifiable patient subgroups have been indicated with regard to the specific use of pemetrexed. However, some poor prognostic indicators have been identified by different groups, such as the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukaemia Group B (CALGB). These indicators include age greater than 75 years, poor performance status and a high white blood cell count. However, there is no particular reason not to offer elderly patients chemotherapy if they are able to tolerate side effects. 2 CancerBACUP is unaware of any data setting out clinically appropriate stopping rules for pemetrexed and cisplatin to treat mesothelioma. However, we would recommend treatment with pemetrexed is continued if it is shown to be effective in prolonging life following a discussion between consultant and patient.	1 and 2 Incorporated in other considerations
RCN	Other considerations	Amongst oncologists there is a variation in opinion about the quality of the research that supports the use of Alimta in mesothlioma and hence the variation in its use. Needless to say patients do their own research and clinicians receive many calls from those wanting to access it and who are currently struggling to do so. Should some consideration be given to patient choice in a non-curative setting?	On para 2, this point has now been included in other considerations
MRC trials	Other	1 Identifiable subgroups are those with different performance status (PS). The survival for those with	1 Already included

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unit	considerations	PS0-1 is significantly better than those with PS2, and it's relevant that the pemetrexed trial only included PS0-1 patients. 2 Response is difficult to measure in mesothelioma patients, and the usual clinical reason for stopping chemotherapy would be obvious signs of progression or excessive toxicity. In mesothelioma, control of the disease, ie stable disease, would be considered a successful result. [This could be categorised as a comment on Stopping Rules, or as an Outcome. AJF]	2 Covered in scope under item on stopping rules.
British Thoracic Soc (late comments)	Various	1 General: treatment is only palliative, not curative 2 Shd say “active supportive care” (ASC), to include radiology 3 Cisplatin not used as monotherapy in the UK, but evidence for use of MVP and single-agent vinorelbine for symptom relief exists. 4 CR-UK trial comparing these drugs with ASC is being carried out. 5 EORTC has conducted trial of raltitrexed and shd be a comparator 6 Subgroups: sarcomatoid malignant mesothelioma would have a worse prognosis 7 Hard to assess response and success of treatment 8 CR-UK trial is the only one providing data about active symptom control. NICE shd try to use any such data for survival and costs, in a non-drug treated group. 9 Use performance status for subgroup analysis 10 Ditto for age at presentation 11 In Background, latency period shd be changed to	1 No action: the scoping document is really only for consultees. Palliation shd be stressed more in later documents that will be read more by the public 2 Scope changed 3 No change because cisplatin was comparator in trial, so must be in the scope. 4 No action. If results available early enough, expect this to be in the evidence base, but not needed in scope 5 Raltitrexed not licensed and not likely to be, so cannot be a comparator.

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		"from 10 years to at least 60 years" 12 Surgery is for at most 1% of patients and no RCT evidence exists that says it is worth doing 13 Change wording about treatments to say they are palliative 14 Minor change in wording	6 Change scope to include as a subgroup 7 Not an action point 8 Reference in "other considerations" 9 Put in scope as a subgroup 10 As for item 9 11 Scope changed accordingly 12 Changes made to scope 13 Suggested wording put in scope 14 Suggested change made to scope.

Statement of 'no comment':

- BOA
- British Lung Foundation
- DoH
- RCGP (which will not be taking part in this appraisal)
- Tenovus