NATIONAL INSTITUTE FOR HEALTH AND 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Eli Lilly	Background	This system has been superseded by the TNM system proposed by the International Mesothelioma Interest Group (Pistolesi et al, 2004).	The evidence quoted in this section uses a different scoring system, that does not mean to say that evidence could not be presented using a different system
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	All changes in bold were added as suggested.

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		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 **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).	Intervention section not altered. The point being made has been put into other considerations.

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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.	This information has been used to inform the comparators section
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.	Added to scope
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	This is acknowledged in the considerations section, in terms of stopping rules for

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		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.	treatments. The outcomes suggested for removal are common outcomes used in oncology trials. The assessment of the evidence will hopefully reveal whether or not they are useful outcomes to consider.
Eli Lilly	Other considerations	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. There are no formal stopping criteria with pemetrexed and as with any palliative treatment, the decision to stop is based upon continuing patient benefit. This is a discussion that should take place between the treating physician, the patient, and their carers	1 Staging defines the appraisal (patients must be resectable) and is not therefore very useful for subgroup analysis 2 Used to inform other 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	1 and 2 Incorporated in other considerations

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		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.	
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 unit	Other considerations	1 Identifiable subgroups are those with different performance status (PS). The survival for those with 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	1 Already included 2 Covered in scope under item on stopping rules.

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		successful result. [This could be categorised as a comment on Stopping Rules, or as an Outcome. AJF]	

Statement of 'no comment':

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