APPENDIX A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Pemetrexed disodium for the treatment of malignant pleural mesothelioma

Final scope

Appraisal objective

To appraise the clinical and cost effectiveness of pemetrexed disodium (Alimta, Eli Lilly) for the treatment of unresectable malignant pleural mesothelioma in chemo-naïve patients, and to provide guidance to the NHS in England and Wales[1,2].

Background

Malignant mesothelioma is a type of cancer which occurs in the mesothelium, a membranous lining which surrounds most internal organs. The mesothelium surrounding the lungs is known as the pleura and the mesothelium in the abdominal cavity is called the peritoneum. Cancers which occur in these lining tissues are named pleural mesothelioma and peritoneal mesothelioma respectively. Over 90% of mesothelioma with a known first site occurs as pleural mesothelioma.

Median survival from diagnosis varies from study to study within a range of 8 to 14 months.

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 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.

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[1]The Department of Health and Welsh Assembly government remit to the Institute: To appraise the clinical and cost effectiveness of pemetrexed disodium for mesothelioma.
[2]Because pemetrexed disodium is licensed only for malignant pleural mesothelioma, the appraisal objective has been amended accordingly.

Surgery is indicated for a small proportion of patients (some 1 to 5%) whose disease is at Stage I or occasionally Stage II using the Butchart staging system[3]. Such patients have a much longer survival rate (15% at 5 years) than patients unsuitable for surgery. For people whose disease has spread, treatments include draining the pleural cavity of excess fluid and applying a talc pleuradhesis (the insertion of talc to prevent further fluid accumulation), radiotherapy either as prophylaxis (following drainage or biopsy) or as palliation of pain or reducing chest wall masses, and chemotherapy.

There appears to be no standard chemotherapy treatment for mesothelioma. Many different combinations of drugs are used, though none is licensed for this indication other than the drug combination under consideration in this appraisal. Agents which have consistently been reported to produce response rates of 10–20% include doxorubicin, epirubicin, mitomycin, cyclophosphamide, ifosfamide, cisplatin, carboplatin, and antifolates.

The technology

Pemetrexed disodium is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pemetrexed disodium in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Cisplatin is a platinum-based chemotherapeutic agent that has antitumour activity, either as a single agent or in combination, for a number of different cancers. It is available in the UK from APS, Mayne and Bristol-Myers Squibb.

In patients treated for malignant pleural mesothelioma, the recommended dose of pemetrexed is 500mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75mg/m2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle.

Intervention(s)	Pemetrexed disodium and cisplatin in combination.
Population(s)	Chemotherapy naive patients with unresectable malignant pleural mesothelioma.

[3] The Butchart staging system has been superseded by the TMN staging system.

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Standard comparators	Cisplatin Other commonly-used alternatives, such as vinorelbine, or MVP (mitomycin C, vinblastine and cisplatin) if data allow Supportive care
Outcomes	The outcome measures to be considered include: • Overall survival • Toxicity and adverse effects of treatment • Symptom palliation • Health-related Quality of Life • Performance status • Tumour response • Progression free survival
Economic analysis	Ideally, the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Costs should be considered from an NHS and Personal Social Services perspective.
Other considerations	• Note that people receiving pemetrexed disodium must also receive folic acid and vitamin B_{12} • Evidence relating to patient choice in a non-curative setting should be considered. • Relevant sub-group analyses (such as performance status and white blood cell count) should be presented if available • Stopping rules for treatment could be explored, and considered in relation to the clinical evidence base and in regard to any economic evaluation • Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: None Related Clinical Guidelines: None