NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Bendamustine for the treatment of non-Hodgkin's lymphoma

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of bendamustine within its licensed indication for the treatment of people with indolent (low grade) non-Hodgkin's lymphoma (NHL) who are refractory to rituximab or a rituximab-containing regimen.

Background

Lymphomas are cancers of the lymphatic system, which is a part of the body's immune system. Traditionally, lymphomas are divided into Hodgkin's disease (now known as Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL). Non-Hodgkin's lymphomas are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease.

Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide. They are termed 'high-grade' (or aggressive) when they divide quickly and 'low-grade' (or indolent) when they divide slowly Indolent lymphomas tend to affect older people. Follicular lymphoma, where the cells are grouped together, is the most common form of NHL, accounting for approximately 30% of all low-grade lymphomas. Precise identification of the form of lymphoma and accurate staging is crucial both for choosing the optimum form of treatment and for monitoring disease progression.

In 2006, 9431 people were diagnosed with non-Hodgkin's lymphoma in England and Wales. The annual incidence of NHL in the UK is approximately 17.4 per 100,000. Survival rates for NHL vary significantly by age. The five-year survival rate for those diagnosed aged 15-44 is 65%, while for those aged 65-74 it is 37%, and for those aged 85 and over it is 13%. In 2007, 4020 people died from non-Hodgkin's lymphoma in England and Wales, reflecting an age standardised mortality rate of 6.5 per 100,000 for men and 4.0 per 100,000 for women. The median survival for people with follicular lymphoma is approximately 10 years.

The clinical presentation, rate of disease progression and patterns of treatment vary widely. Low-grade lymphomas often grow very slowly and there may be long periods where there is very little, or no, change in the disease. For many people, regular check-ups are often the most appropriate option (known as active surveillance or watchful waiting), with appropriate interventions when symptoms develop. There may be multiple episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type.

The aim of current management is to achieve the best possible remission for the longest period, and to prolong survival. First-line treatment for limited indolent NHL usually consists of radiotherapy to the affected lymph nodes. First-line treatment for advanced indolent NHL includes single-agent chemotherapy, such as chlorambucil, fludarabine or cyclophosphamide. Combination chemotherapy regimens with or without steroids and/or a monoclonal antibody (rituximab) is also an option for first-line treatment of advanced indolent NHL. Second-line treatments include single-agent chemotherapy and combination chemotherapy (with or without steroids and/or rituximab). Subsequent therapy options include rituximab monotherapy, or high-dose chemotherapy with stem cell support.

The technology

Bendamustine (brand name unknown, Napp Pharmaceuticals) is an alkylating antitumour agent. The drug and its derivatives break down into alkyl groups which bond with substances inside tumour cells, resulting in impaired DNA functions and cell death. It is administered by intravenous infusion.

Bendamustine does not currently have a UK marketing authorisation. Bendamustine has been studied in a single arm clinical trial in people with indolent NHL who are refractory to rituximab or a rituximab-containing regimen.

Intervention(s)	Bendamustine
Population(s)	People with indolent non-Hodgkin's lymphoma who are refractory to rituximab or a rituximab-containing regimen

Comparators	• Single agent chemotherapy including:
	  ○ Fludarabine
	  ○ Cyclophosphamide
	  ○ Chlorambucil
	• Combination chemotherapy regimens including:
	  ○ Cyclophosphamide, vincristine and prednisolone (CVP)
	  ○ Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
	  ○ Fludarabine, doxorubicin and dexamethasone
	  ○ Fludarabine, mitoxantrone and dexamethasone

Outcomes	The outcome measures to be considered include: • response rates • duration of response/remission • time to new anti-lymphoma treatment/ time to progression • overall survival • adverse effects of treatment • health related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 137, February 2008, 'Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of technology appraisal guidance 37).' Review date: December 2010. Technology Appraisal No. 65, September 2003, 'Rituximab for aggressive non-Hodgkin's lymphoma'. Review date: August 2006. Technology Appraisal No. 110, September 2006, 'Rituximab for the treatment of follicular lymphoma'. Review date: June 2009. Technology Appraisal in Preparation, 'Rituximab within its licensed indication for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Temsirolimus for the treatment of relapsed or refractory mantle cell lymphoma'. Earliest anticipated date of publication September 2010. Related Guidelines: Clinical Guideline No. CSGHO, October 2003, 'Improving outcomes in haemato-oncology cancer (expected review date TBC).

Questions for consultation

What line of treatment is bendamustine likely to be used for?

Should the remit, population and comparators be further defined by the stage of NHL?

Have the most appropriate comparators been included in the scope?

- Have the most appropriate single and combination therapies been included as comparators?
- Should best supportive care be included as a comparator?
- Should radiotherapy be included as a comparator?

Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)