NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma.

Background

Lymphomas are cancers of the lymphatic system. They are broadly divided into Hodgkin's lymphoma and non-Hodgkin's lymphomas. Non-Hodgkin's lymphoma can be divided into low grade and aggressive lymphomas. Low-grade (also called 'indolent') lymphomas are slow growing, with long median survival times but are less likely to be cured by treatment. Follicular lymphoma is a low-grade lymphoma of B-lymphocytes and accounts for approximately 30% of all low-grade lymphomas.

Precise identification of the type of lymphoma and accurate staging of the disease is crucial both for choosing the optimum treatment and for monitoring disease progression. The stage of non-Hodgkin's lymphoma reflects how many groups of lymph nodes are affected, where they are in the body, and whether other organs such as the bone marrow or liver are affected. One of the most common systems for classifying non-Hodgkin's lymphoma identifies four stages. Early follicular lymphoma includes stages I and II, and advanced disease includes stages III and IV. In stage I, only one group of lymph nodes in one organ of the body is affected. In stage II, the disease has spread to two lymph groups on the same side of the diaphragm. Stage III disease includes lymph nodes affected on both sides of the diaphragm, and stage IV of the disease usually involves multiple internal organs, for example, the liver, bone marrow, or blood.

Non-Hodgkin's lymphoma accounts for approximately 4% of all cancers diagnosed in the UK, with 9431 new cases registered in England and Wales in 2006, and 4011 registered deaths in 2007. Depending on the classification system used, between 22% and 40% of non-Hodgkin's lymphomas are follicular. The incidence of follicular lymphoma increases with age, with the median age at diagnosis between 60 and 65 years. Over 70% of people with follicular lymphoma are still alive 5 years after the diagnosis, with median survival over 10 years. Most people will have disease at stage III or IV at the time of diagnosis.

For many people regular check-ups are the most appropriate clinical management (known as active surveillance or watchful waiting) until active treatment is needed when symptoms develop. There may be many episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type. Treatment for low-grade non-Hodgkin's lymphoma can lead to partial remission (decrease the size of the lymphoma, or reduce the extent of lymphoma in the body) or to complete remission (when the disease is not detectable anymore).

The aim of management is to achieve the longest possible remission and improve quality of life. Despite a long median survival, follicular lymphoma is generally considered incurable. First-line treatment for advanced indolent non-Hodgkin's lymphoma includes single-agent chemotherapy, such as chlorambucil, fludarabine or cyclophosphamide. Combination chemotherapy regimens may be used as first or second line treatment options and include CVP (cyclophosphamide, vincristine and the steroid prednisolone), and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), often in combination with the biological therapy rituximab (R-CVP and R-CHOP). Fludarabine based chemotherapy combinations may also be given such as FAD (fludarabine, doxorubicin, and the steroid dexamethasone) and FMD (fludarabine, mitoxantrone and dexamethasone). Subsequent therapy options include rituximab monotherapy, or high-dose chemotherapy with stem cell support.

NICE Technology Appraisal No. 110 recommends R-CVP as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients. In addition, NICE Technology Appraisal No. 137 recommends rituximab in combination with chemotherapy as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma. Technology Appraisal No. 137 also recommends rituximab monotherapy as: 1) maintenance therapy as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab, and 2) an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

The technology

Bortezomib (Velcade, Janssen-Cilag) is an anticancer drug that works by reversible proteasome inhibition. By inhibiting proteasomes, multi-enzyme complexes present in all cells, bortezomib interferes with the cell cycle leading to cell death.

Bortezomib does not currently have a UK marketing authorisation for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma. It is being studied in clinical trials in combination with rituximab in people with

relapsed or refractory, rituximab naive or sensitive, follicular B-cell non-Hodgkin's lymphoma, compared with rituximab alone.

Intervention(s)	Bortezomib in combination with rituximab.
Population(s)	People with relapsed or refractory follicular non-Hodgkin's lymphoma.
Comparators	Comparison will be made with: • Fludarabine in combination with mitoxantrone and dexamethasone (FMD) or in combination with doxorubicin and dexamethasone (FDD). • Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), with or without rituximab (R-CHOP). • Cyclophosphamide, vincristine and prednisolone (CVP) with or without rituximab (R-CVP). • Rituximab monotherapy
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rates • duration of disease remission • 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 marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.110, Sept 2006, 'Rituximab

	for the treatment of follicular lymphoma. Update in progress, earliest anticipated date of publication: TBC. 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, Sept 2003, 'Rituximab for non-Hodgkin´s lymphoma'. Appraisal on static list since 2006. Technology appraisal in preparation, 'Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy'. Earliest anticipated date of publication: January 2011. Technology Appraisal in preparation, 'Bendamustine for the treatment of people with indolent (low grade) non-Hodgkin's lymphoma who are refractory to rituximab or a rituximab-containing regimen'. Earliest anticipated date of publication: TBC. Related Guidelines: Clinical Guideline No. CSGHO, October 2003, 'Improving outcomes in haemato-oncology cancer.

Questions for consultation

Have the most appropriate comparators for bortezomib in the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma been included in the scope? Are the comparators listed routinely used in clinical practice?

Are there any subgroups of people in whom bortezomib 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?

Do you consider bortezomib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of bortezomib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

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)