NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

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

Draft scope

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 70% of all low-grade lymphomas and 22-35% of all non-Hodgkin's lymphomas.

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. In stage I, one group of lymph nodes in one area 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 10,917 new cases registered in England and Wales in 2007, and 4438 registered deaths in 2008. 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, improve quality of life, and to extend overall survival. 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), usually 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.

A review of NICE Technology Appraisal No. 110, which will be published at the end of January 2012, recommends R-CVP, R-CHOP, R-MCP (mitoxantrone, chlorambucil and prednisolone), R-CHVPi (cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α) and rituximab in combination with chlorambucil as options 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). NICE Technology Appraisal No. 226 recommends rituximab maintenance therapy as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

The technology

Bortezomib (Velcade, Janssen) 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 is administered as an intravenous injection.

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)	Adults with relapsed or refractory follicular non-Hodgkin's lymphoma.

Comparators	Comparison will be made with:
	• Single or multiple agent chemotherapy including
	  ○ Chlorambucil (with or without rituximab)
	  ○ Fludarabine, cyclophosphamide, and rituximab (FCR)
	  ○ Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)
	  ○ Rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CVP)
	• Rituximab monotherapy

Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rates • duration of disease remission • time to next therapy • 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. Under review. 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). Appraisal on static list since March 2011. Technology Appraisal No.65, Sept 2003, 'Rituximab for non-Hodgkin´s lymphoma'. Appraisal on static list since 2006. Technology appraisal No. 226, June 2011, 'Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma'. Review date: May 2014. Technology Appraisal No. 206, October 2010 (terminated), 'Bendamustine for the treatment of people with indolent (low grade) non-Hodgkin's lymphoma who are refractory to rituximab or a rituximab-containing regimen'. Technology Appraisal in preparation, 'Bendamustine in combination with rituximab for the first-line treatment of indolent non-Hodgkin's lymphoma', Earliest anticipated date of publication: TBC. Related Guidelines: Clinical Guideline No. CSGHO, October 2003, 'Improving outcomes in haemato-oncology cancer.

Questions for consultation

Given that bortezomib will be given in combination with rituximab, would it be reasonable to compare it with single agent chemotherapy *without* rituximab?

Please define single agent chemotherapy for the purpose of this appraisal.

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

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not

share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider the technology 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 the technology 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.