NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Bortezomib for induction and consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of bortezomib within its licensed indications as 1) induction treatment for people with newly diagnosed multiple myeloma, and 2) as consolidation therapy after autologous stem cell transplantation for people with multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody that does not work properly and is not able to fight infection. Myeloma cells build up in the bone marrow and interfere with the production of normal blood cells, which are responsible for blood clotting, carrying oxygen around the body and fighting infections. They also have the ability to spread throughout the bone marrow and into the hard outer casing of the bone. The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

About 3900 people were diagnosed with multiple myeloma in England and Wales in 2008. It is most frequently diagnosed in people aged 70–79 years and is uncommon in young people (fewer than 2% of diagnoses are in people less than 40 years old). Multiple myeloma is more common in men than in women. Average survival for people with multiple myeloma is between 4 and 6 years, but ranges from a few weeks to more than 20 years.

Multiple myeloma is an incurable disease. The aim of therapy is to achieve stable disease for as long as possible, thereby prolonging survival and maximising quality of life. Aggressive first-line treatment with high-dose chemotherapy (usually melphalan) followed by stem cell transplantation may be considered for people in good general health. However, before high-dose chemotherapy is administered, induction therapy should be given with an aim to induce high remission rates rapidly, and with minimal toxicity, and to preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells. After induction therapy, haematopoietic stem cells are harvested before high-dose chemotherapy is administered. The harvested stem cells are stored and then reintroduced to the patient's blood (autologous stem cell transplants) following chemotherapy. This enables the bone marrow

to recover quickly, so it can produce healthy blood cells again. In 2008, approximately 820 autologous stem cell transplants were conducted in the UK for people with multiple myeloma (that is, approximately 20% of all people newly diagnosed that year).

In the current management of multiple myeloma, induction regimens should contain at least one novel agent (thalidomide, bortezomib or lenalidomide). The most commonly used induction regimen in UK clinical practice is thalidomide in combination with cyclophosphamide and dexamethasone (CTD), however other regimens such as thalidomide in combination with dexamethasone and doxorubicin (TAD), bortezomib in combination with dexamethasone, and bortezomib in combination with doxorubicin and dexamethasone (PAD) are also used. Decisions regarding the most appropriate induction treatment for individual patients will require the assessment of a number of factors such as renal function, thrombotic risk and pre-existing neuropathy.

Following stem cell transplantation, all patients receive ongoing monitoring and supportive care. In some people, active consolidation (maintenance) treatment may be considered, with the aim of stimulating the immune system and slowing or stopping cancer cell growth. In the past, interferon alpha and corticosteroids (such as prednisolone and dexamethasone) were used in this way, but their use is no longer recommended. In current practice, thalidomide and bortezomib may be considered for a minority of patients. However, there is currently no standard consolidation treatment routinely used in the NHS.

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. It is administered by intravenous infusion.

Bortezomib does not currently have a UK marketing authorisation for induction therapy or for consolidation therapy following autologous stem cell transplantation in people with multiple myeloma. It is being studied in clinical trials as induction therapy in combination with several different chemotherapy regimens including alternating cycles of vincristine, carmustine melphalan, cyclophosphamide and prednisone (VBMCP), and vincristine, doxorubicin and dexamethasone (VAD) compared with alternating cycles of VBMCP-VAD alone in people with newly diagnosed multiple myeloma who have not received any prior therapy. It is also being studied as induction therapy in combination with doxorubicin and dexamethasone, compared with combination therapy with vincristine, doxorubicin and dexamethasone; and in combination with thalidomide and dexamethasone compared with thalidomide alone. In all trials, participants receive high dose chemotherapy (namely melphalan) and autologous stem cell transplantation after induction therapy.

Bortezomib is also being studied in clinical trials as consolidation monotherapy compared with no treatment in people with multiple myeloma who have received high-dose melphalan and autologous stem cell transplantation as a first-line treatment.

Bortezomib has a UK marketing authorisation for use in combination with chemotherapy (melphalan and prednisone) for the treatment of people with multiple myeloma who have not received prior therapy and who are not eligible for high-dose chemotherapy with bone marrow transplantation. It also has a UK marketing authorisation as monotherapy for the treatment of multiple myeloma that has progressed despite the use of at least one prior therapy and where the individual has already undergone or is unsuitable for bone marrow transplantation.

Interventions	• Induction therapy: Bortezomib in combination with an optimum chemotherapy regimen • Consolidation therapy: Bortezomib monotherapy
Populations	• Induction therapy: Adults with newly diagnosed multiple myeloma who have not received prior treatment and who are suitable for autologous stem cell transplantation • Consolidation therapy: Adults with newly diagnosed multiple myeloma who have had autologous stem cell transplantation
Comparators	Induction therapy: For people with newly diagnosed multiple who have not received prior treatment and who are receiving bortezomib as induction therapy: • Optimum chemotherapy regimens containing one novel agent (such as thalidomide in combination with cyclophosphamide and dexamethasone; thalidomide in combination with dexamethasone and doxorubicin) Consolidation therapy: For people with newly diagnosed multiple myeloma who have had autologous stem cell transplantation: • Best supportive care (‘watchful waiting’) • Lenalidomide (subject to ongoing NICE appraisal)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • time to progression • response rates • 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. 228, July 2011, 'Bortezomib and thalidomide for the first line treatment of multiple myeloma'. Expected review date July 2014. Technology Appraisal in Preparation, 'Lenalidomide for the treatment of newly diagnosed multiple myeloma'. Earliest anticipated date of publication January 2013. Technology Appraisal in Preparation, 'Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation'. Earliest anticipated date of publication December 2012. Related Guidelines: Cancer Service Guidance, October 2003, Improving Outcomes in Haematological Cancer.

Questions for consultation

Have the most appropriate comparators for bortezomib as induction and consolidation therapy for the treatment of multiple myeloma for people who

are suitable for autologous stem cell transplantation been included in the scope?

- Are the comparators listed routinely used in clinical practice?

- Are chemotherapy regimens without a novel agent (such as vincristine-doxorubicin-dexamethasone) still routinely used in UK clinical practice as induction therapy?

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.

Should NICE appraise the two proposed indications for bortezomib (induction and consolidation therapy) through its Single Technology Appraisal (STA) or Multiple Technology Appraisal (MTA) process? If the STA process is considered more appropriate, should this appraisal be divided into two separate STAs (that is, should induction and consolidation therapy be considered separately)? 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)