NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Vorinostat in combination with bortezomib for the treatment of multiple myeloma in people who have received at least one prior therapy

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of vorinostat in combination with bortezomib within its licensed indication for the treatment of multiple myeloma in people who have received at least one prior therapy.

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 4000 people were diagnosed with multiple myeloma in England and Wales in 2008. It is most frequently diagnosed in people aged 70–79 and is uncommon in young people (fewer than 2% of new cases involve people less than 40 years old). Multiple myeloma is more common in men than in women and the incidence may also be higher in people of African and Caribbean family origin. Average survival for people with multiple myeloma is between 3 and 5 years, but survival can range from a few weeks to more than 20 years.

Multiple myeloma is an incurable disease. The aim of therapy is to achieve as long a period of stable disease as possible, thereby prolonging survival and maximising quality of life. Aggressive initial treatment, in the form of high-dose chemotherapy with stem-cell transplantation, may be possible for people in good general health. Other first-line treatment options include single-agent or combination therapies which may include thalidomide or bortezomib, alkylating agents (melphalan, cyclophosphamide), and corticosteroids (prednisolone, dexamethasone).

Following initial treatment, people with multiple myeloma usually experience a period of remission, but disease will eventually relapse – that is, become refractory (unresponsive) to treatment. For some other people, the disease never responds to first-line treatment. Choice of therapy at this stage is influenced by previous treatment and response to it, duration of remission, comorbidities, patient preference and cytogenetic markers of disease. Repeat high-dose chemotherapy with stem-cell rescue may be considered for some individuals. NICE technology appraisal guidance No. 129 recommends bortezomib monotherapy as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation. NICE technology appraisal guidance No. 171 recommends lenalidomide in combination with dexamethasone as a possible treatment for people with multiple myeloma who have received at least two prior therapies. Other treatment options may include chemotherapy with alkylating agents and anthracyclines, thalidomide and corticosteroids (alone or in combination use).

The technology

Vorinostat (Zolinza, Merck Sharp & Dohme) is an oral histone deacetylase inhibitor that alters histone proteins as well as non-histone proteins, leading to changes in chromatin structure. This in turn leads to changes in protein synthesis and inhibition of tumour growth. One of the genes most commonly induced by vorinostat encodes p21, an inhibitor of cell proliferation.

Vorinostat does not currently have a UK marketing authorisation for the treatment of multiple myeloma. Vorinostat has been studied in combination with bortezomib in comparison with bortezomib and placebo. People in the trial were required to have progressive disease after the failure of at least one but not more than three antimyeloma regimens. Potential trial participants were excluded if they had previously undergone bone-marrow transplantation or if such treatment was planned for them.

Intervention(s)	Vorinostat in combination with bortezomib
Population(s)	Adults with multiple myeloma who have received at least one prior therapy, and have not undergone and are not suitable for bone-marrow transplantation.
Comparators	The comparators to be considered are: • bortezomib monotherapy and bortezomib in combination with high-dose dexamethasone • lenalidomide in combination with high-dose dexamethasone

	• thalidomide-containing regimens • repeat initial chemotherapy, including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin • high-dose dexamethasone monotherapy
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival and/or 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	If the evidence allows, subgroups including the following will be considered: • populations according to number of prior antimyeloma therapies • people who have previously received bortezomib Details of the effective cost of the included drugs as a result of any risk sharing schemes or patient access schemes should be sought and made available to the manufacturer submitting evidence. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 129, October 2007, 'Bortezomib monotherapy for relapsed multiple

	myeloma.' Review date: Mid 2011. Technology Appraisal No. 171, June 2009, 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy.' Review date: Mid 2011. Technology Appraisal in Preparation, 'Bortezomib and thalidomide for the first-line treatment of multiple myeloma.' Earliest anticipated date of publication: TBC. Related Guidelines: Cancer Service Guidance, October 2003, 'Improving Outcomes in Haematological Cancer.'

Questions for consultation

Has the intervention been defined correctly? In particular:

- Would vorinostat plus bortezomib be used in combination with high-dose dexamethasone in clinical practice?

Has the population been defined correctly? In particular:

- Would prior bone-marrow transplantation be considered a contraindication to vorinostat plus bortezomib in clinical practice?

Have the most appropriate comparators for the treatment of multiple myeloma in people who have received at least one prior therapy been included in the scope? Are the comparators listed routinely used in clinical practice? In particular:

- Is bortezomib routinely used in combination with high-dose dexamethasone in clinical practice?
- Is it possible to specify more precisely the chemotherapeutic regimen(s) which would be considered in this population?
- Are thalidomide-containing regimens routinely used in second- and subsequent-line treatment of multiple myeloma?
- Would high-dose dexamethasone monotherapy be used in people for whom vorinostat plus bortezomib is suitable?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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

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)