NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bortezomib for the treatment of multiple myeloma

Response to non consultee/commentator health professionals on the main issues from consultation on the Appraisal Consultation Document

Main themes of comments on the ACD	Place where considered in the Final Appraisal Determination
The technology	
Bortezomib is a long-awaited major, innovative advance in treatment of myeloma. It has a novel mode of action and is active in patients who are refractory to other therapies.	The Appraisal Committee was aware that bortezomib works through a novel mechanism and accepted that bortezomib monotherapy is more clinically effective than HDD monotherapy , see FAD section 2.1, 4.2 and 4.3.
Consideration of the evidence	
clarity of treatment pathway	
There are clearly defined treatment pathways for myeloma and over the course of the disease patients will receive different combinations of treatment at different times. The treatment is clearly described in the BCSH and UK/Nordic guidelines.	The position of bortezomib in the pathway of care is discussed in paragraph 4.2 of the FAD.
Lack of consensus is a feeble basis on which to deny bortezomib, there will always be some controversy, particularly in this heterogenous, relapsing, remitting disease.	Any inconsistency in clinical opinion would be relevant for the choice of comparator in the economic modelling. The position of bortezomib in the pathway of care is discussed in FAD section 4.2.
position of bortezomib in treatment pathway	
There is no doubt that bortezomib has an important place in the treatment of relapse multiple myeloma. Bortezomib needs to be available as a treatment option.	The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness. Any new treatments recommended should be cost effective compared with existing treatments.

The APEX trial defines the position of bortezomib in myeloma.	The position of bortezomib in the pathway of care is discussed in FAD section 4.2, and the Appraisal Committee's considerations of the clinical and cost effectiveness of its use at first relapse are discussed in FAD sections 4.4 to 4.8.
Bortezomib should be available to patients at all relapses in accordance with the marketing authorisation.	
Bortezomib is used at first relapse in patients who have received thalidomide, and at second relapse in patients who are thalidomide naive.	
Bortezomib should at least be available to patients at first relapse.	
Bortezomib should at least be available to patients who have relapsed or are unsuitable for several treatment options and therefore have little or no choice (with good performance status).	
The decision of which patients should receive bortezomib should be made by doctors and patients.	NICE has been requested by the Department of Health to provide guidance on the clinical and cost effectiveness of bortezomib for the treatment of multiple myeloma. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5).
comparators	
HDD is clearly an appropriate comparator and is the most appropriate choice.	The Appraisal Committee agreed that HDD is an appropriate comparator (see FAD section 4.2), but that other comparators are also clinically relevant (see FAD section 4.10).
Thalidomide is unlicensed, unproven, has significant side effects and is costly.	Alternative treatments to bortezomib are discussed in FAD section 4.10.
An increasing proportion of patients receive thalidomide (now >70%) as first-line treatment (this is related to the MRC myeloma IX study).	
Retreatment with induction chemotherapy has results inferior to initial treatment.	
Repeat stem cell transplant is only available to a small minority of patients, and may be associated with considerable cost, morbidity and is of unproven benefit.	

evidence of clinical effectiveness of bortezomib	
The clinical benefit of bortezomib is unquestionable, and proven beyond any reasonable doubt. APEX study is level 1 evidence.	The Appraisal Committee agreed that there is clear trial evidence that bortezomib monotherapy is more clinically effective than HDD monotherapy, see FAD section 4.2 and 4.3
The aim of treatment in this incurable disease is to improve the quality and duration of life. The results achieved with bortezomib are remarkable and highly important to patients. The toxic profile is of no major concern.	Comments noted.
combination use with dexamethasone	
Bortezomib is not most efficiently used as monotherapy. It is common practice to use bortezomib in combination with intermediate doses of dexamethasone, which studies have shown to increase response rates and survival benefit.	The Appraisal Committee considered the use of bortezomib in combination with dexamethasone and other drugs, see FAD sections 4.9 and 4.10 of the FAD. Guidance is given by NICE within the boundaries of the marketing authorisation. See Guide to the Methods of Technology Appraisal http://www.nice.org.uk/page.aspx?o=201973, section 6.1.6.
quality of life improvement	
Bortezomib can be given on an outpatient basis, enabling patients to remain at home. It can provide better disease control. This can improve and maintain patients' quality of life.	Comments noted.
adverse effects	
Bortezomib treatment is generally well tolerated. It is associated with a lower rate of infection and bone destruction.	The Appraisal Committee considered the adverse effects associated with bortezomib compared with HDD, see FAD paragraph 4.3.
drug costs	
Stopping of treatment in non-responders is clinically appropriate, already occurs in practice, and improves cost-effectiveness. The majority of patients have a tumour marker which enables physicians to assess	The Appraisal Committee considered the clinical and cost effectiveness of stopping bortezomib treatment in non-responders after a limited number of cycles, see FAD section 4.6.

response to disease in a simple and timely fashion.	
Vial sharing has been performed successfully in practice, can dramatically improve cost effectiveness. A smaller, cheaper vial is needed.	The Appraisal Committee considered a scenario in which vial sharing was adopted as a more cost effective use of bortezomib, see FAD section 4.8.
Bortezomib is an expensive treatment, and careful consideration is taken in prescribing it.	Comment noted.
No account has been taken of the cost saving from dose reduction which is used after adverse events and reduces drug costs.	Adverse effects were not included in the economic model, either in terms of effects on quality of life or resource use. The manufacturer's comments on the ACD included results from a revised economic model in which costs related to adverse events were modelled, see FAD section 3.6, 4.6 and 4.7.
costs of other care	
Bortezomib can decrease inpatient admissions, is quick to administer and requires minimal nursing time.	Comment noted.
cost-driven decision	
The treatment is being declined on the grounds of cost, and the decision is unethical if cost is the driving factor	The Committee does not consider the affordability, that is, costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). Any new treatments recommended should be cost effective compared with existing treatments.
Implementation	
Effective use of bortezomib in relapse myeloma can be implemented through already established national and local pathways (UKMF/BCSH guidelines group, cancer networks, site specific groups and MDTs).	Comment noted.

Proposed recommendations for further research	
Clinical trials involving bortezomib are valuable & are encouraged	
Further clinical trials are not necessary	
It is unethical to restrict the use of bortezomib to only patients enrolled in trials. By only making bortezomib available to patients in trials, large numbers of myeloma sufferers will be denied a drug that could prolong their lives and give improved quality of life. - only a minority (10%) of patients will be able to receive bortezomib in clinical trials - many will not meet eligibility criteria or do not live near a trial centre - funding for participating in trials may not be met by PCTs - new trials will take a long time to set up, and funding may be difficult to obtain	} Amendments have been made in the FAD. See sections 1.1, 4.10, 4.11 and 6.1.
It is not ethical to for patients to be entered into a clinical trial where they may not receive what we know to be the best drug available to them. The draft guidance put patients under pressure to enter trials and this is unethical.	
Full funding should follow this guidance from the NHS/Department of Health.	
Myeloma IX: - is the only current national study - enrols at diagnosis and it is due to close soon so few patients at relapse will gain access to bortezomib through myeloma IX - will not provide answers relevant to this appraisal as bortezomib is used in combination with dexamethasone, and there is no randomisation at relapse	
Further research interest is in the efficacy of bortezomib as first line treatment, its performance in combination with other treatments, and identification of myelomas most likely to respond to targeted therapy.	
Related guidance (erythropoietin for anaemia induced by cancer treatment)	
NICE has a poor track record for haematological malignancies. Erythropoietin can be used to treat anaemia caused by myeloma.	Comment noted.

Proposed date for review of guidance	
Three years is too long, particularly for a patient group with short life expectancy. If the recommendations do not change, review should be in 12 months, maximum 18 months.	This date has been amended, see FAD. section 8.2.
Inequality	
The decision is particularly unfair because patients in other parts of the UK have access to bortezomib	Comment noted.
The decision will perpetuate the existing postcode lottery within England and Wales	Comment noted.
Myeloma patients in the England and Wales will have inferior treatment and a poorer prognosis than those in other European countries and the USA.	Comment noted.
Myeloma patients are being put at a lower priority than other patients (eg, breast cancer)	The appraisal process, methodology and decision criteria are the same for all appraisals. See Guide to the Methods of Technology Appraisal (Available from URL http://www.nice.org.uk/page.aspx?o=201974)

NICE Secretariat
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