NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of TA129; Bortezomib monotherapy for relapsed multiple myeloma and TA171; Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy

TA129 was issued in October 2007 and TA171 in June 2009.

A decision was made by the Institute's Guidance Executive in October 2010 to defer the review date for both pieces of guidance to mid-2011. This was subsequently deferred to the present date in order to allow discussions to take place with the Department of Health regarding the patient access schemes relating to both these technologies.

Background

At the GE meeting of 21 February 2012 it was agreed that we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	Both pieces of guidance should be transferred to the 'static guidance list'.
Rationale for selecting this proposal	The literature search did not identify any new published clinical evidence which is likely to lead to a change in the recommendations in previous guidance. No changes to existing patient access schemes are currently proposed and no other guidance is in development.

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	TA129 should be transferred to the 'static guidance list. TA171 recommends treatment with lenalidomide only in people who have received two or more prior therapies, and no need to review this recommendation has been highlighted by consultees. This recommendation can therefore be placed on the 'static list'. The marketing authorisation also includes lenalidomide treatment after one prior therapy, which was not considered cost effective during the development of TA 171 and was therefore not included in the recommendation in TA171. A part review of TA171 should be planned into the appraisal work programme as an STA to specifically address the treatment with lenalidomide after one prior therapy with bortezomib. This is because NICE has recently recommended first-line treatment with bortezomib in TA228 for people who are unable to tolerate or have contraindications to thalidomide. First line treatment with bortezomib was not an option when TA171 was developed. Updated survival analysis is available for lenalidomide and the currently existing patient access scheme was not explored for second line treatment.

Respondent	**Response to proposal**	**Details**	**Comment from Technology Appraisals**
Healthcare Improvement Scotland	No comment	Healthcare Improvement Scotland has no comment to make on the proposal to move TA129 and TA171 to the Static List and we have noted this accordingly in our records.	Response noted. No action required
GlaxoSmithKline	No objection	We have no objection to TAGs 129 and 171 being moved to the static list.	Comment noted. No action required
Royal College of Pathologists / British Society for	No objection	The Royal College of Pathologists and BSH have no evidence to submit on the above appraisal.	Comment noted. No action required

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Haematology			
Royal College of Nursing	No objection	Nurses caring for people with myeloma were invited to review the proposal to move the above guidance to the static list. The proposal seems appropriate. There are no further comments to submit at this stage on behalf of the Royal College of Nursing.	Comment noted. No action required
Celgene	Disagree	Celgene's position remains unchanged from an earlier response. Our view is that TA171 should be updated to recognize that as a consequence of TA228 (bortezomib and thalidomide for the first line treatment of multiple myeloma) there is a subset of patients for whom there is no reimbursed treatment option, barring a retreatment with bortezomib which may not be clinically appropriate. Celgene therefore believes that lenalidomide which already holds a marketing aurthorisation for treatment of myeloma patients after 1 prior therapy should be considered as an alternative for this subset of patients. The proposal to move the review of TA 171 to a static list essentially leaves a cohort of patients with no treatment option after relapsing on bortezomib and it is disappointing that the Institute has failed to take into consideration the impact of its own recommendation set out in TA228 for	TA 228 recommends bortezomib (in combination with an alkylating agent and a corticosteroid) for the first-line treatment of multiple myeloma for patients in whom high-dose chemotherapy with stem cell transplantation is considered inappropriate and thalidomide is contraindicated or untolerated. It is therefore anticipated that bortezomib is used for a small subset of patients in the first line setting. In TA171 the Committee agreed that the ICER for 2nd line lenalidomide compared with dexamethasone would be higher than £69,000 per QALY gained (TA171 sections 4.11 and 4.12). The effect of the current patient access scheme on this ICER has not been established.

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		bortezomib as a first line option for patients with newly diagnosed multiple myeloma. In TA 171, the Committee reached a view that the use of lenalidomide at second-line was not a cost-effective use of NHS resources. Crucially, the comparator in this analysis included bortezomib. However, since bortezomib is now recommended as a treatment option for newly diagnosed patients, the appropriate comparator for lenalidomide at second line has changed. As a result, the cost-effectiveness evidence considered by the Committee in TA 171 is no longer relevant and the decision reached with respect to lenalidomide requires updating. Furthermore approval for the use of lenalidomide through the Cancer Drug Fund (CDF) indicates that there indeed is a clinical need for the use of lenalidomide at second line. Whilst the CDF has been instituted as a means to address some of unmet clinical need, a reliance on it alone will not be sufficient and in fact may result in increased geographical variation in access to appropriate treatments. Celgene recognizes that significant resources are required to conduct full HTA reviews and NICE is operating in a highly resource-constrained environment. However the current review process	In the cost effectiveness analysis referred to by the consultee, evidence of the effectiveness was derived from a subgroup analysis of the MM-009/010 trials of 241 patients who had received one prior therapy (high dose chemotherapy plus stem cell transplantation, thalidomide or bortezomib). It remains unclear how many of these received bortezomib as the first line treatment. It should be noted that in the M009/M010 trials only 54 patients had received prior bortezomib therapy (which may be first line or subsequent) out of a total of 504 patients in the pooled analysis. The uncertainty around the clinical effectiveness of lenalidomide after prior treatment with bortezomib needs to be carefully considered. The issue of funding through CDF is not relevant for a technology appraisal review decision.

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		is deficient and we hope that NICE will take a pragmatic approach and conduct some form of a rapid review which will ensure that the existing guidance TA171 for lenalidomide remains relevant and informative.	
Merck Sharp and Dohme	No comment	MSD Ltd do not have any comments on the proposal.	Response noted. No action required
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Cancer Physicians	Agree	Our experts would be happy for this appraisal to be moved to the static list.	Comment noted. No action required
Janssen	Agree	Janssen is supportive of this decision and we can confirm that there is no new evidence, supporting the intravenous and subcutaneous injections of bortezomib monotherapy or bortezomib-based combinations for the treatment of relapsed multiple myeloma, than the one previously communicated.	Comment noted. No action required
Myeloma UK	Disagree	Whilst we appreciate that, due to time constraints and limited resources, NICE cannot consider all its	Comments noted.

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		workload high-priority, we do believe that a review of TA129 should be factored into the NICE work programme to ensure that the guidance is up-to-date and relevant to myeloma clinical practice in the NHS. Myeloma is a complex and multi-factorial cancer, and for this reason treatment with a combination of drugs is widely accepted to be more effective than using monotherapy. The British Committee for Standards in Haematology (BCSH) and the UK Myeloma Forum (UKMF) Guidelines on 'The Diagnosis and Management of Multiple Myeloma' highlight that 'single-agent activity of novel agents is limited and these agents should normally be given in combination to maximise benefits' (2010). In the case of bortezomib, both clinical trial data and UK clinical practice show that the effectiveness of bortezomib is increased when given in combination with the steroid dexamethasone. Whilst not included within its European marketing licence, in the UK bortezomib is almost always provided in combination with dexamethasone. This is on the basis of strong clinical trial data, expert clinical judgement and patient level evidence of	NICE can only appraise drugs in line with the marketing authorisation from the European Medicines Agency (EMA) or Medicines and Healthcare Products Regulatory Agency (MHRA).

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		efficacy. The BCSH and UKMF guidelines also that state that, 'unless contraindicated, treatment with thalidomide, bortezomib or lenalidomide treatment should be delivered with dexamethasone +/- chemotherapy to increase the response rate'. Hideshima et al (2001) first found evidence to show an additive anti-proliferative effect when bortezomib was combined with dexamethasone. To support this finding, the results of the SUMMIT trial outlined by Richardson et al (2003) found that in the study 18% of relapsed myeloma patients who had a suboptimal response to bortezomib monotherapy showed an improved response when dexamethasone was added alongside the treatment. Data provided by Jagannath et al (2004) also showed that when dexamethasone was added to bortezomib monotherapy in relapsed myeloma patients the overall response rate of participants increased from 33% to 44% (in patients who received 1.0mg of bortezomib) and from 50% to 62% (in patients who received 1.3mg of bortezomib). A post-hoc study by Jagannath et al (2006) also confirmed these findings. Whilst this data is not 'new evidence' per se, when it is taken in combination with the consensus of	NICE is aware of the widespread use of off label combination therapy with dexamethasone. Therefore, the impact of any potential NICE recommendation for combination therapy could only be limited, and therefore NICE guidance could not be considered to add value.

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		myeloma expert opinion, it provides a strong picture to support the addition of dexamethasone into NICE TA129 to improve the relevance of the guidance to NHS clinical practice. **Subcutaneous Velcade** The NICE review recommendation states that the results of a study on subcutaneous Velcade demonstrated that it 'offers a similar efficacy to standard intravenous administration, with an improved safety profile' (Moreau et al 2011). Subcutaneous bortezomib has recently been granted a licence by the US FDA and is expected to receive a similarly positive recommendation from the EMA in the coming months. Whilst NICE has accepted that the data on subcutaneous bortezomib is strong, the review recommendation states that if this administration method receives an EU marketing licence, it will result in a decrease the ICER but is unlikely to result in an overall change to the guidance. Whilst at Myeloma UK we understand that the NICE guidance is unlikely to be affected overall, we do believe that it would be beneficial to patients for NICE to include a recommendation in TA129 about the use of subcutaneous bortezomib in myeloma patients.	NICE guidance refers to summary of product characteristics (SPC) for details on drug use, route of administration, dosing regimen etc. NICE believe inclusion of subcutaneous route of administration in SPC would not change the current NICE guidance. NICE will only update guidance when there is a strong expectation that the recommendation would change in light of the new evidence or new formulation. It would not be justifiable use of scarce NHS resources to carry out an update of positive appraisal recommendations in order to address an implementation issue.

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		Subcutaneous bortezomib has been an important development and innovation in the treatment of myeloma, as it reduces the level of side-effects that patients receiving bortezomib experience – in particular peripheral neuropathy. If NICE make a supportive recommendation in NICE TA129 about the use of subcutaneous bortezomib, this would increase the speed and quantity of its uptake at local commissioning level. It would also ensure that patents are not precluded access to subcutaneous administration of bortezomib at local level due to a lack of formal NICE guidance. As subcutaneous bortezomib has not yet been granted a European marketing licence, it may be necessary to delay a review of TA129 until a final decision has been made by the EMA. However, we do know that it is already becoming a more common method of administration for bortezomib in myeloma patients.	

No response received from:

<u>Patient/carer groups</u> • Afiya Trust • Black Health Agency • Cancer 52	<u>General</u> • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission

- Cancer Black Care
- Cancer Equality
- Counsel and Care
- Equalities National Council
- Helen Rollason Heal Cancer Charity
- Leukaemia CARE
- Leukaemia Society UK
- Macmillan Cancer Support
- Maggie's Centres
- Marie Curie Cancer Care
- Muslim Council of Britain
- Muslim Health Network
- Rarer Cancers Foundation
- South Asian Health Foundation
- Specialised Healthcare Alliance
- Tenovus

<u>Professional groups</u>

- British Association for Services to the Elderly
- British Committee for Standardisation in Haematology
- British Geriatrics Society
- British Institute for Radiology
- British Psychosocial Oncology Society
- British Society for Blood and Marrow Transplantation
- Cancer Network Pharmacists Forum
- Cancer Research UK
- NHS Blood and Transplant
- Royal College of General Practitioners
- Royal Pharmaceutical Society
- Royal Society of Medicine
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency
- National Association of Primary Care
- National Pharmacy Association
- NHS Alliance
- NHS Commercial Medicines Unit
- NHS Confederation
- Public Health Wales NHS Trust
- Scottish Medicines Consortium

<u>Comparator manufacturers</u>

- Aspen Europe GmbH (melphalan)
- Baxter Healthcare (cyclophosphamide)
- Bristol-Myers Squibb (carmustine)
- Celgene (thalidomide)
- Genus Pharmaceuticals (vincristine)
- Hameln Pharmaceuticals (doxorubicin)
- Hospira UK (doxorubicin, vincristine)
- Laboratories Genopharm (melphalan)
- Medac GmbH (doxorubicin)
- Pfizer (cyclophosphamide, doxorubicin, idarubicin)
- Teva UK (vincristine)
- Wockhardt UK (doxorubicin)

<u>Relevant research groups</u>

- Cochrane Haematological Malignancies Group
- Elimination of Leukaemia Fund
- Leukaemia and Lymphoma Research

• Society and College of Radiographers • UK Myeloma Forum • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • NHS Bassetlaw • NHS Bedfordshire • Welsh Government	• Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Network • National Institute for Health Research • Research Institute of the Care of Older People <u>Assessment Group</u> • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • None

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