National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Myeloma UK	We consider the background information contained in the draft scope to be largely accurate, particularly the description of myeloma. However, there are a few accuracy points for NICE to consider including: • The patient population for whom TA171 is designed to cover is not clearly defined in the background information • Despite being approved as a monotherapy in TA129, bortezomib (Velcade®) for myeloma patients at first relapse is almost always prescribed in combination with dexamethasone in clinical practice • The background information contains information about the response criteria for bortezomib, which appears fairly randomly within the text. This should expressly state that it is part of the Velcade Response Scheme for context • Specific reference should be made to the patient access scheme (PAS), the Revlimid Response Scheme, accepted as part of TA171 • The background omits to mention that the end-of-life modifiers were also applied to TA171, as well as the PAS	Comments noted. Please note that the background section is only intended to provide a brief overview of the disease and its associated management. Please also note that this section includes wording taken from existing published technology appraisals for multiple myeloma.
	Celgene Ltd, UK & Ireland	The background information given in the scope is accurate for consultation purposes and Celgene has no other comments to add	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.

Section	Consultees	Comments	Action
	National Cancer Research Institute /Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	No comments.	Comment noted. No action required.
	Royal College of Pathologists/British Committee for Standards in Haematology	No comments	Comment noted. No action required.
	UK Myeloma Forum	No comments	Comment noted. No action required.
The technology/ intervention	Myeloma UK	We consider the description of the technology accurate.	Comment noted. No action required.
	Celgene Ltd, UK & Ireland	In addition to the description provided, Celgene requests that the following be included - "Lenalidomide inhibits proliferation of certain haematopoietic tumour cells, enhances T cell- and Natural Killer (NK) cell-mediated immunity, increases foetal haemoglobin production by CD34+ haematopoietic stem cells and inhibits production of pro-inflammatory cytokines. Lenalidomide is administered orally."	Comment noted. This section is intended to provide only a brief and simple description of the technology. The technology section has been updated.

Section	Consultees	Comments	Action
	Janssen	No comment.	Comment noted. No action required.
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	This is accurate.	Comment noted. No action required.
	Royal College of Pathologists/British Committee for Standards in Haematology	This is accurate	Comment noted. No action required.
	UK Myeloma Forum	This is accurate	Comment noted. No action required.

Section	Consultees	Comments	Action
Population	Myeloma UK	We consider this to be a vague definition of the patient population which would benefit significantly from clarification. It is important that NICE accurately define the patient population relevant to this appraisal and whether it applies only to myeloma patients who have received bortezomib upfront in line with TA 228 (i.e. those intolerant/contraindicated to thalidomide) and for whom bortezomib is an inappropriate or sub-optimal treatment at first relapse (in line with TA129) or whether the patient population has wider application. This wider application, which could be interpreted from the patient population specified in the scope, could include myeloma patients: • who have received bortezomib at first-line as part of clinical study and who would not be suitable for bortezomib repeat treatment at first relapse • Who had received bortezomib as part of their induction treatment prior to high-dose therapy and stem cell transplantation via the Cancer Drug Fund • Patients who received bortezomib because of renal impairment at presentation but for whom bortezomib would not be an option at first relapse • Patients with severe peripheral neuropathy for whom repeat treatment with a peripheral neuropathy-causing drug would be contraindicated Despite these described subsets being a very small group of patients, from a Myeloma UK perspective it is nonetheless a very important group that is deserving of access to optimal treatment at first relapse; especially those who have taken part in clinical studies at diagnosis. This is something that <u>should</u> be discussed and agreed before finalising the scope.	Comment noted. This appraisal is for the use of lenalidomide for people with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib. The population section has been updated.

Section	Consultees	Comments	Action
	Celgene Ltd, UK & Ireland	To be more specfic, Celgene requests the population to be defined as "adults with multiple myeloma whose disease has progressed after an initial prior treatment with bortezomib."	Comment noted. The population section has been revised.
	Janssen	No comment.	Comment noted. No action required.
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	This is appropriate.	Comment noted. No action required.
	Royal College of Pathologists/British Committee for Standards in Haematology	This is appropriate.	Comment noted. No action required.
	UK Myeloma Forum	This is appropriate.	Comment noted. No action required.

Section	Consultees	Comments	Action
Comparators	Myeloma UK	It is impossible to say for sure what the most appropriate comparators should be until the patient population is more clearly defined (see note above). However, current standard treatment options in clinical practice in this setting would broadly include: - Bortezomib in combination with dexamethasone (although very unlikely that dexamethasone would be given in high doses) - Standard chemotherapy combinations based on melphalan, bendamustine (via nCDF), vincristine, cyclophosphamide and doxorubicin - A thalidomide-based combination - Lenalidomide via nCDF High-dose dexamethasone <u>is not</u> an appropriate comparator. These should be discussed and agreed when the patient population has been clearly defined.	Comment noted. The comparators section has now been updated. For the population included in this appraisal, thalidomide would be contraindicated.

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<tr><th>Section</th><th>Consultees</th><th>Comments</th><th>Action</th></tr>
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<td></td>
<td>Celgene Ltd, UK & Ireland</td>
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The treatment pathway for multiple myeloma has evolved with the advent of proteasome inhibitors and immunomodulatory agents plus more recent label extensions of existing agents within the pathway.

Recent data published by NHS England (http://www.england.nhs.uk/2013/08/12/cancer-drugs-fund-list/) and shown in the table below indicates that retreatment with bortezomib is now a clinically supported practice and therefore can be considered as an appropriate comparator for this appraisal.

Standard chemotherapy agents including bendamustine are also used to a limited extent; however the ability to make any reasonable comparison would be contingent on the level of evidence base available.

<table>
<tr><th>Drug</th><th>CDF - MM Indication</th><th>Total Notifi cations</th></tr>
<tr><td>Bendamustine</td><td>Treatment of relapsed multiple myeloma where other treatments are not appropriate</td><td>73</td></tr>
<tr><td>Bortezomib</td><td>Treatment of relapsed or refractory multiple myeloma at second and subsequent relapse in patients with previous good response to bortezomib</td><td>34</td></tr>
<tr><td>Lenalidomide</td><td>2nd line treatment of multiple myeloma in patients who have contraindications to the use of bortezomib</td><td>24</td></tr>
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High dose dexamethasone (HDD) is rarely used now in the setting being appraised by NICE and even if used is typically considered and reserved as a last resort treatment option for a very limited number of patients. HDD therefore cannot be considered as a comparator as it is inconsistent with current UK clinical practice
</td>
<td>Comment noted. The comparators section has now been updated.

For the population included in this appraisal, thalidomide would be contraindicated.</td>
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Section	Consultees	Comments	Action
	Janssen	Market research commissioned by Janssen indicates that, after bortezomib as the 1st line treatment, the following therapies are used as the 2nd line treatment for multiple myeloma in the UK; • Bortezomib-based regimen (i.e. retreatment with bortezomib) • Thalidomide • Lenalidomide • Bendamustine We suggest bortezomib-based regimen, thalidomide and bendamustine be included in the list of comparators due to their significant market shares (each with approximately 10% or above) in the relevant patient population in the UK.	Comment noted. The comparators section has now been updated. For the population included in this appraisal, thalidomide would be contraindicated.
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	An additional comparator should be thalidomide. It is most commonly used with steroids and an alkylating agent. High dose dexamethasone is not an appropriate comparator, it is seldom used at this stage of the disease	Comment noted. The comparators section has now been updated. For the population included in this appraisal, thalidomide would be contraindicated.

Section	Consultees	Comments	Action
	Royal College of Pathologists/British Committee for Standards in Haematology	An additional comparator would be thalidomide, that is most commonly used with steroids and cyclophosphamide. High dose dexamethasone is not an appropriate comparator, it is seldom used at this stage of the disease.	Comment noted. The comparators section has now been updated. For the population included in this appraisal, thalidomide would be contraindicated.
	UK Myeloma Forum	An additional comparator would be thalidomide, that is most commonly used with steroids and cyclophosphamide. High dose dexamethasone is not an appropriate comparator, it is seldom used at this stage of the disease.	Comment noted. The comparators section has now been updated. For the population included in this appraisal, thalidomide would be contraindicated.
Outcomes	Myeloma UK	We agree that these are the most important outcomes measures for this appraisal.	Comment noted. No action required.
	Celgene Ltd, UK & Ireland	Yes	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.

Section	Consultees	Comments	Action
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	An additional outcome should be: Time to next treatment.	Comment noted. The outcomes section has been updated.
	Royal College of Pathologists/British Committee for Standards in Haematology	An additional outcome should be: Time to next treatment.	Comment noted. The outcomes section has been updated.
	UK Myeloma Forum	An additional outcome should be: Time to next treatment.	Comment noted. The outcomes section has been updated.
Economic analysis	Myeloma UK	No comments	Comment noted. No action required.
	Celgene Ltd, UK & Ireland	A life-time model will be appropriate for this economic analysis.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.

Section	Consultees	Comments	Action
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	No comment	Comment noted. No action required.
	Royal College of Pathologists/British Committee for Standards in Haematology	No comment	Comment noted. No action required.
	UK Myeloma Forum	No comment	
Equality and Diversity	Myeloma UK	No comments	Comment noted. No action required.
	Celgene Ltd, UK & Ireland	Celgene has no comments to add here.	Comment noted. No action required.

Section	Consultees	Comments	Action
	Janssen	No comment.	Comment noted. No action required.
Innovation	Myeloma UK	There is currently a significant unmet need for myeloma patients at first relapse who received bortezomib in the frontline setting and for whom repeat treatment may not be optimal at first relapse. The use of lenalidomide in this setting would be innovative and has the ability to substantially improve outcomes in this group of patients who would otherwise be almost certainly sub-optimally treated.	Comment noted. The potential innovative nature of the technology would be considered as part of any future appraisal.
	Celgene Ltd, UK & Ireland	Lenalidomide is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment. This can be of immense help to patients who have mobility problems. However this benefit is unlikely to be reflected in the standard QALY measure.	Comment noted. The potential innovative nature of the technology would be considered as part of any future appraisal.
	Janssen	No comment.	Comment noted. No action required.

Section	Consultees	Comments	Action
	National Cancer Research Institute / Royal College of Physicians /Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	The technology is innovative in the treatment of this group of patients. It belongs to the IMiD group of drugs, that have potent anti-myeloma activity, and has a different side effect profile to other available myeloma therapies.	Comment noted. The potential innovative nature of the technology would be considered as part of any future appraisal.
	Royal College of Pathologists/British Committee for Standards in Haematology	The technology is innovative in the treatment of this group of patients. It belongs to the IMiD group of drugs, that have potent anti-myeloma activity, but unlike thalidomide, the toxicity profile is more tolerable, allowing patients to receive adequate treatment in a timely fashion.	Comment noted. The potential innovative nature of the technology would be considered as part of any future appraisal.
	UK Myeloma Forum	The technology is innovative in the treatment of this group of patients. It belongs to the IMiD group of drugs, that have potent anti-myeloma activity, but unlike thalidomide, the toxicity profile is more tolerable, allowing patients to receive adequate treatment in a timely fashion.	Comment noted. The potential innovative nature of the technology would be considered as part of any future appraisal.
Other considerations	Myeloma UK	No comments	Comment noted. No action required.

Section	Consultees	Comments	Action
	Celgene Ltd, UK & Ireland	The patient population eligible for treatment with lenaliomide following an initial treatment with bortezomib is a small cohort of approximately 300 patients in the UK. NICE has already issued a guidance for lenalidomide treatment after 2 prior therapies. The clinical evidence base for lenalidomide for treatment after 1 prior therapy has not changed. However, with the treatment pathway having evolved, the comparator has changed. As a consequence of more patients receiving bortezomib at front line in the contemporary treatment pathway, an unmet need has resulted , with no NICE recommended option for these patients.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
Questions for consultation	Myeloma UK	• Patients who receive bortezomib in the upfront (newly diagnosed) setting, in line with NICE TA228, may benefit from repeat treatment with bortezomib at relapse if they achieved an optimum response to the treatment • Patients who receive bortezomib in the upfront setting on the NHS and do not achieve an optimum response, would either be contraindicated to repeat treatment with bortezomib or are likely to receive a poor response and risk additional side-effects that may prohibit the use of future treatments • There needs to be additional licensed treatment options available at each stage of relapse to account for the heterogenic presentation of patients and based on prior treatment responses • The sub-group of patients that would benefit from this indication are those that have received bortezomib in any upfront setting and for which retreatment with bortezomib is considered suboptimal	Comments noted. Bortezomib will remain as a comparator. The subgroup suggested is the population of interest in this appraisal.
	Celgene Ltd, UK & Ireland	No comments	Comment noted. No action required.

Section	Consultees	Comments	Action
	Janssen	Please see above for our comment on the list of relevant comparators.	Comment noted. No action required.
	Royal College of Pathologists/British Committee for Standards in Haematology	Patients who have received prior treatment with bortezomib and who have had a good and durable response may receive an additional line of therapy with bortezomib, as they are likely to derive further benefit from bortezomib. For patients whose disease has progressed following treatment with bortezomib, chemotherapy regimens would include the comparators already listed, plus thalidomide regimens.	Comments noted. Bortezomib will remain as a comparator. For the population included in this appraisal, thalidomide would be contraindicated.
	UK Myeloma Forum	Patients who have received prior treatment with bortezomib and who have had a good and durable response may receive an additional line of therapy with bortezomib, as they are likely to derive further benefit from bortezomib. For patients whose disease has progressed following treatment with bortezomib, chemotherapy regimens would include the comparators already listed, plus thalidomide regimens.	Comments noted. Bortezomib will remain as a comparator. For the population included in this appraisal, thalidomide would be contraindicated.
Additional comments on the draft scope.	Myeloma UK	We have one final comments on the draft scope for the consideration of NICE: Whilst the CDF in England has approved the use of lenalidomide in this setting for myeloma patients, we welcome the commitment of NICE to review NICE TA171 and to work towards providing sustainable access to lenalidomide for myeloma patients in this setting We look forward to exploring these issues with NICE at the pending scoping workshop.	Comment noted. No action required.
	Celgene Ltd, UK & Ireland	No Comments	Comment noted. No action required.
	Janssen	No further comment.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Merck Sharp & Dohme
Department of Health
Royal College of Nursing