Single technology appraisal (STA)
Lenalidomide for multiple myeloma in people who have received at least one prior therapy

Janssen-Cilag's comments on the ACD

i) Do you consider that all of the relevant evidence has been taken into account?

We consider that the relevant published evidence to date has been taken into account.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Janssen-Cilag fully supports the need for patients with multiple myeloma to have access to the latest and most effective treatment options. Given the devastating nature of this condition, we agree that it was appropriate to consider the evidence based for lenalidomide in the context of the recent end of life arrangements.

In reviewing the provisional recommendations of the Appraisal Committee, we believe that some of the details regarding the patient access scheme require further clarification.

Firstly, we believe that the current threshold at which free of charge medicines would be provided is unclear as written. As a result we would like to request clarification of the treatment duration during which the NHS will cover the cost. As currently written, the guidance is open to interpretation on the following points:

- Is it the two years of treatment that is most important, or the total number of cycles? For example, is the free of charge supply intended to become available after 2 years of continuous treatment (defined as 26 cycles of 28 days), or would free of charge supply be provided later than 2 years after starting treatment in the event that patients had breaks in their treatment. This would have the effect of spreading the 26 cycles over a period longer than 2 years and allowing retreatment with lenalidomide.
- The assessment of clinical benefit and provisional recommendation has been based on MM009 and MM010 RCTs in which lenalidomide was continued until the occurrence of disease progression or unacceptable toxic effects. To prevent any confusion with the funding arrangements where two years of treatment is discussed we would like to suggest specifying that treatment is to be continued until disease progression.

Secondly, we note that free of charge medication is only provided after two years/26 cycles of treatment (+£100,000 of costs to the NHS) and yet the median duration of treatment is less than

one year. We wonder whether the extent to which the NHS will benefit from these arrangements has been fully assessed.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

We are not aware of any specific equity related issues.

Additional comments.

- The ACD for this guidance is entitled as follows

'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy'.

Given that the recommendation now only applies to second relapse and beyond, we believe that this title has the potential to be confusing as it refers to the population who has received "at least one prior therapy".

We would suggest amending the title to reflect the population for which lenalidomide is recommended in this 2nd ACD: 'Lenalidomide for the treatment of multiple myeloma in people who have received two or more prior therapies'.

- The ACD states page 5 under section 3.1:

'For people in whom bortezomib was contraindicated, for people who had received two or more prior therapies and for people who had received prior thalidomide (only one or two or more prior therapies) the comparator was dexamethasone'

It is assumed that the contraindications NICE is referring to in the paragraph above are the ones indicated in the SPC* of Velcade® and which are copied below for convenience:

- Hypersensitivity to bortezomib, boron or to any of the excipients.
- Severe hepatic impairment.
- Acute diffuse infiltrative pulmonary and pericardial disease

Velcade® is not contraindicated in patients with peripheral neuropathy.
The SPC† states: 'Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment.'
Also in the SPC*, recommendation is made to 'carefully monitor for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified'.

- The ACD states page 15 under section 4.4:

* http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=17109

† http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=17109

'Current NICE guidance restricts the use of bortezomib to first relapse because the use of bortezomib at subsequent relapses was found not to be cost-effective (NICE technology appraisal guidance 129), with ICERs of £77,000 or more per QALY gained.'
We would like to point out that at the time of the appraisal of bortezomib for relapse myeloma (1st relapse and relapse/refractory) the supplemental advice from NICE for the appraisal of life extending medicines was not available yet. Therefore we would like to propose the inclusion of the following sentence to reflect the fact that the appraisal of bortezomib for relapse myeloma was undertaken under different circumstances than the one of lenalidomide. The added section is underlined below.
'Current NICE guidance restricts the use of bortezomib to first relapse because the use of bortezomib at subsequent relapses was found not to be cost-effective (NICE technology appraisal guidance 129 – October 2007), with ICERs of £77,000 or more per QALY gained without the application of the Velcade Response Scheme. This appraisal of bortezomib was undertaken prior to the publication of NICE's supplemental advice for the appraisal of life-extending medicines.

- The ACD states page 16 under section 4.7:

'It noted that from patients' viewpoint lenalidomide is associated with a more favourable adverse effect profile than most other regimens and agents used in the management of relapsed multiple myeloma.'

Given that lenalidomide has only been available for a relatively short period of time, Janssen-Cilag Ltd believes that the safety profile of lenalidomide has yet to be fully determined.
As the statement is unsubstantiated and may be prejudicial against other regimens and agents given the lack of any robust comparison, head to head RCTs or observational studies, we would like to request that this is removed.

- The ACD states page 16-17 under section 4.7:

'It heard from clinical specialists and patient experts that lenalidomide might be particularly useful for people with pre-existing peripheral neuropathy in whom the use of bortezomib at first relapse is restricted. '

- We would like to point out that an ongoing prospective study by Dimopoulos et al[*]. has showed that 27% of patients with grade ≥ 2 pre-existing peripheral neuropathy receiving Revlimid and Dexamethasone (RD) experienced a deterioration of neuropathy.
  Also the SPC of lenalidomide indicates that Peripheral neuropathy is a common adverse drug reaction observed in patients treated with lenalidomide/dexamethasone:

- As the above statement does not reflect the SPC* of Velcade® we would suggest specifying after the statement made by clinical specialists and patient experts that the SPC does not include any restriction for patients with pre-existing neuropathy. The SPC

[*] Reference: *Meletios A. Dimopoulos et al.* Treatment of Patients with Relapsed/Refractory Multiple Myeloma (MM) with Lenalidomide and Dexamethasone with or with Bortezomib Depending on Prior Neurotoxicity: Prospective Evaluation of the Impact of Cytogenetic Abnormalities and Assessment of Bone Met. To be presented on December 6th, 2008 - American Society of Hematology Meeting – December 6-9, 2008, San Francisco, USA. http://ash.confex.com/ash/2008/webprogram/Paper3409.html

states: ’Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment’.
Also in the SPC, a recommendation is made to carefully monitor for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified