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; in addition we would like to recommend the consideration of the study by Dimopoulos et al[*]. to be published/ presented on December 6th 2008 at the American Society of Hematology Meeting.

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, and that the preliminary views on the resource impact and implications for the NHS are appropriate

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?

We consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

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

No comment

Separate comments:

- The ACD states page 5 under section 3.1:

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

It is understood 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.

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[*] 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

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

- 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 14 under section 4.6:

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

- 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 states: 'Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment'.

  Also in the SPC (please see paragraph below), 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

Under the Peripheral Neuropathy section the SPC* states:
'Treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.
It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of VELCADE to be modified (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Improvement in, or resolution of, peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the single agent phase III multiple myeloma study and 71%

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

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of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase II studies, respectively.
In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.'