**Indication:**
NICE approved indication for bortezomib:
Second line therapy for patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.

PAD is indicated in the following clinical situations:
- Primary refractory disease if transplant suitable candidate
- Relapsed disease if considering transplant
- Relapsed disease if requires rapid cytoreduction e.g. renal failure

The use of bortezomib outside NICE (i.e. not as second line therapy for patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation) must be agreed as per the local process for managing and funding unapproved regimens.

Consider avoiding use in patients with pre-existing severe neuropathy.

**Regimen details:**

**PAD bolus doxorubicin:**
- **Bortezomib** 1.3 mg/m² IV Days 1, 4, 8, 11
- There must be a minimum of 72 hours between doses.
- **Doxorubicin** 9 mg/m² IV Days 1, 2, 3, 4
- **Dexamethasone** 20 mg od orally Days 1, 4, 8, 11

**PAD 4 day infusional doxorubicin:**
- **Bortezomib** 1.3 mg/m² IV Days 1, 5, 9, 12
- There must be a minimum of 72 hours between doses.
- **Doxorubicin** 9 mg/m² IV Days 1, 2, 3, 4 (this is a continuous infusion, i.e. 36 mg/m² over 96 hours)
- **Dexamethasone** 20 mg od orally Days 1, 5, 9, 12

**Administration:**
- Bortezomib IV bolus over 3 to 5 seconds
- Doxorubicin IV bolus or continuous 96 hour infusion

**Premedication:**
- Non required

**Frequency:**
- 21 day cycle, maximum of 6 cycles (Consider previous anthracycline treatment; maximum cumulative lifetime dose 550 mg/m²)
- Assess response after each cycle (by EBMT criteria)
- If VGPR or greater after 2 cycles then stop.
- If < VGPR after 3 cycles, give 4 cycles.
- Minimal response (MR), no change (NC) or progressive disease at 4 cycles, stop treatment.
- Progressive disease at any point, stop treatment.

**Extravasation:**
- Bortezomib: Non-vesicant

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**Reason for Update:** Network Protocol Development

**Version:** 1

**Supersedes:** All other versions

**Prepared by:** Laura Cameron

**Approved by Consultant:** Matthew Streetly

**Approved by Chair Haem TWG:** Maj Kazmi

**Date:** 25/02/2011

**Checked by (Network Pharmacist):** Jacky Turner
Doxorubicin: Vesicant

Anti-emetics: Mild emetogenicity

Supportive Care:
- Antiviral prophylaxis as per local policy e.g. aciclovir 200mg bd
- PPI or H2-receptor antagonist e.g. omeprazole 20mg od if receiving dexamethasone
- Allopurinol 300mg od (or 100mg od for renal impairment) for first cycle only
- Consider antifungal prophylaxis as per local protocol if the patient is also receiving dexamethasone
- 250ml sodium chloride 0.9% over 30 minutes is administered prior to each dose of bortezomib to minimise any symptoms of postural hypotension.

To manage peripheral neuropathy:
- Consider Vitamin B and folic acid supplementation
- Topical cocoa butter (not supplied by NHS) applied to affected areas twice a day may be beneficial to some patients
- Gabapentin up to 300mg tds for neuropathic pain
- Further details as per SELCN Guidelines for the Management of Multiple Myeloma and Related Plasma Cell Disorders

Regular investigations:
- FBC D1, 4/5, 8/9 and 11/12
- LFTs D1
- U&Es D1
- Serum paraprotein and serum free light chains at the start of each cycle.

NB Paraprotein levels MUST be recorded on the chemotherapy proforma, including the percentage reduction from baseline.
- Baseline neurological examination.
- Baseline vitamin B12 and folate.

Toxicities:
- Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation
- Hepatobiliary disorders. The most common haematological toxicity is thrombocytopenia.
- Peripheral neuropathy. Orthostatic/postural hypotension. Cardiotoxicity – patients with a known history of heart disease, should have an Echo prior to commencing treatment.
- Fatigue. Tumour lysis syndrome. Rash.

Dose Modifications

Haematological Toxicity

<table>
<thead>
<tr>
<th>Reason for Update: Network Protocol Development</th>
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<tbody>
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Bortezomib, Doxorubicin & Dexamethasone (PAD) for Multiple Myeloma

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Version: 1 Approved by Chair Haem TWG: Maj Kazmi
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Prepared by: Laura Cameron Checked by (Network Pharmacist): Jacky Turner

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the, day 1 dose will go ahead even if neutrophils <1.0 x 10^9/L and platelets < 75 x 10^9/L. This should be confirmed with a Consultant

Prior to every cycle of PAD:

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Bortezomib &amp; Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0 x 10^9/L</td>
<td>&amp;</td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt;1.0 x 10^9/L</td>
<td>or</td>
<td>Delay on a weekly basis, until recovery of toxicity.</td>
</tr>
</tbody>
</table>

If neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), delay until as above, and reduce the bortezomib dose to 1 mg/m^2 and the doxorubicin dose to 6 mg/m^2 for all further cycles.

If further toxicity occurs where neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1, delay until as above, and reduce the bortezomib dose to 0.7 mg/m^2 and the doxorubicin dose to 4.5 mg/m^2 for all further cycles.

Prior to any day of bortezomib during a cycle (other than D1):

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Bortezomib &amp; Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.75 x 10^9/L</td>
<td>&amp;</td>
<td>100% dose</td>
</tr>
<tr>
<td>&lt; 0.75 x 10^9/L</td>
<td>or</td>
<td>With hold until recovery of toxicity. Re-initiate treatment at a reduced dose.</td>
</tr>
</tbody>
</table>

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the doses will go ahead even if neutrophils < 0.75 x 10^9/L and platelets < 30 x 10^9/L. This should be confirmed with a Consultant.

If neutrophils < 0.75 x 10^9/L and platelets < 30 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), delay until as above, and reduce the bortezomib dose to 0.7 mg/m^2 and the doxorubicin dose to 4.5 mg/m^2 for all further cycles.

Doses not given in a cycle are not made up later.

Consideration should be given to platelet transfusion and GCSF support for haematological toxicity. This must be on the recommendation of a Consultant Haematologist.

Renal Impairment
Bortezomib should be used with caution in patients with CrCl < 20ml/min not undergoing dialysis; however, no specific dosing recommendations have been made. Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.

Hepatic Impairment
There is very limited information available regarding the use of bortezomib in patients with hepatic insufficiency and it should therefore be used with caution. Discuss the use of doxorubicin if bilirubin > 30 umol/L and/or ALT/AST > 2.5 ULN.

Non-Haematological toxicities

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paraesthesia, weakness and/or loss of</td>
<td>No action</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 with pain or 2 (interfering with function but not with activities of daily living)</td>
<td>Reduce to 1.0 mg/m²</td>
<td></td>
</tr>
<tr>
<td>2 with pain or 3 (interfering with activities of daily living)</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate bortezomib treatment and reduce dose to 0.7 mg/m² and change treatment schedule to once per week.</td>
<td></td>
</tr>
<tr>
<td>4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) and/or severe autonomic neuropathy</td>
<td>Discontinue bortezomib</td>
<td></td>
</tr>
</tbody>
</table>

Doses reduced for toxicity should not be re-escalated

Drug interactions: Bortezomib may increase the levels/effects of citalopram, phenytoin and other CYP2C19 substrates. Levels/effects of bortezomib may be increased by azole antifungals, ciprofloxacin, clarithromycin, erythromycin, verapamil and other CYP3A4 inhibitors.