Subcutaneous Bortezomib (Velcade®), Melphalan, Prednisolone (VMP) for Multiple Myeloma

Indication:
- First line therapy for patients who
  - are unsuitable for stem cell transplantation and are unable to tolerate or have contraindications to thalidomide
  - are unsuitable for stem cell transplantation and present with renal impairment (CrCl < 30ml/min)

Regimen details:
- **Twice weekly protocol:**
  - Bortezomib 1.3 mg/m² SC Days 1, 4, 8, 11
  - Melphalan 7mg/m²* orally Days 1 to 4
  - Prednisolone 60mg/m² orally Days 1 to 4

- **Weekly protocol:**
  - Bortezomib 1.3 mg/m² SC Days 1, 8, 15, 22
  - Melphalan 7mg/m²* orally Days 1 to 4
  - Prednisolone 60mg/m² orally Days 1 to 4

  * Consider capping the melphalan dose at 10mg.

Administration:
- Bortezomib subcutaneous bolus over 3 to 5 seconds
- The site of subcutaneous injection should be rotated between the thighs and abdomen.
- Melphalan and prednisolone orally.

Premedication:
- None required

Frequency:
- Twice weekly protocol:
  - 21 day cycle for up to 8 cycles

- Weekly protocol:
  - 5-week cycle for up to 8 cycles

Assess response after each cycle (by EBMT criteria)
- If complete response (CR) is achieved, give another 2 cycles and stop.
- If partial response (PR) or PR plateau is achieved, give another 2 cycles. These responding patients who do not achieve a CR can receive up to 8 cycles.
- Minimal response (MR), no change (NC) or progressive disease at 4 cycles, stop treatment.

Extravasation:
- Non-vesicant

Anti-emetics:
- Mild emetogenicity

Reason for Update: SC route licensed, include twice weekly protocol
Approved by Consultant: M Streetly 09/12/2012

Version: 2
Approved by Chair Haem TWG: M Kazmi

Supersedes: All other versions
Date: 17/12/2012

Prepared by: Laura Cameron
Checked by (Network Pharmacist): J Turner 12/12/2012
**Supportive Care:**
- Antiviral prophylaxis as per local policy e.g. aciclovir 200mg bd
- PCP prophylaxis as per local policy e.g. co-trimoxazole 960mg od Monday, Wednesday and Friday each week
- Consider antifungal prophylaxis as per local policy
- PPI or H₂ receptor antagonist as per local policy
- Allopurinol 300mg od (or 100mg od for renal impairment) for first cycle only / until plateau
- 500ml oral hydration prior to the bortezomib dose

To manage peripheral neuropathy:
- Vitamin B compound strong, one tablet once a day
  (NB one Vitamin B compound strong tablet contains: 20mg nicotinamide, 2mg pyridoxine, 2mg riboflavin, 5mg thiamine)
- Folic acid 5mg once a week
- Cocoa butter (not supplied from NHS) applied to affected areas twice a day
- Gabapentin up to 300mg tds for neuropathic pain

**Regular investigations:**
- FBC D1 and prior to each bortezomib dose
- LFTs D1
- U&Es D1
- Serum paraprotein and serum free light chains at the start of each cycle.
- 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

Prior to every cycle of VMP (twice weekly and weekly):

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0 x 10⁹/L &amp; ≥ 70 x 10⁹/L</td>
<td>100% dose</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 x 10⁹/L or &lt; 70 x 10⁹/L</td>
<td>Delay on a weekly basis, until recovery of toxicity.</td>
<td></td>
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</table>

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the cycle 1 day 1 dose will go ahead even if neutrophils <1.0 x 10⁹/L and platelets < 70 x 10⁹/L. This should be confirmed with a Consultant.

If neutrophils < 1.0 x 10⁹/L and platelets < 70 x 10⁹/L on day 1 of subsequent cycles (when previously > than these levels), delay until as above, and reduce the bortezomib dose to 1.0 mg/m² for all further cycles.

If further toxicity occurs where neutrophils < 1.0 x 10⁹/L and platelets < 70 x 10⁹/L on day 1, delay until as above, and reduce the bortezomib dose to 0.7 mg/m² for all further cycles.
Prior to any day of bortezomib during a cycle (other than D1):

<table>
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<tr>
<th>Neutrophils</th>
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<tbody>
<tr>
<td>≥ 0.5 x 10⁹/L &amp; ≥ 30 x 10⁹/L</td>
<td>100% dose</td>
<td></td>
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<tr>
<td>&lt; 0.5 x 10⁹/L or &lt; 30 x 10⁹/L</td>
<td>With hold until recovery of toxicity. Re-initiate treatment at a reduced dose. If several bortezomib doses in a cycle are withheld (≥ 2 doses) bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²)</td>
<td></td>
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NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the doses will go ahead even if neutrophils < 0.5 x 10⁹/L and platelets < 30 x 10⁹/L. This should be confirmed with a Consultant.

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.

**Melphalan:**
- SeCr < 177 µmol/L: 100% dose
- SeCr > 177 µmol/L: reduce melphalan dose by 50%
- SeCr > 354 µmol/L: Discuss with Consultant

**Hepatic Impairment**

There is very limited information available regarding the use of bortezomib or melphalan in patients with hepatic insufficiency and therefore VMP should be used with caution.

**Non-Haematological toxicities**

<table>
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<tr>
<th>Severity of neuropathy</th>
<th>Bortezomib</th>
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<tbody>
<tr>
<td>Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)</td>
<td>Reduce to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 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>
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<tr>
<td>Grade 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>
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Prednisolone may be dose reduced for corticosteroid toxicities

### 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 byazole antifungals, ciprofloxacin, clarithromycin, erythromycin, verapamil and other CYP3A4 inhibitors. During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetes.

**References:**
- [www.medicines.org.uk](http://www.medicines.org.uk)
- Personal communication with Paul Richardson
  Mateos M-V. *et al.* 2006 Bortezomib plus Melphalan and Prednisolone in Elderly Untreated Patients with Multiple Myeloma: Results of a muticentre phase 1/2 study. Blood 108:2165-2172
  A Phase 3 Prospective Randomized International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib in patients with Relapsed Multiple Myeloma. Moreau P *et al.* ASH 2010 Abstract number 312
  NICE TA 228 July 2011 Bortezomib and thalidomide for the first-line treatment of multiple myeloma

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