## Drug Administration Schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4, 8, &amp; 11</td>
<td>Bortezomib</td>
<td>1.3mg/m²</td>
<td>IV bolus/SC injection*</td>
<td>None</td>
<td>Fast bolus: 3 to 5 seconds</td>
</tr>
<tr>
<td>1 to 28</td>
<td>Thalidomide</td>
<td>Escalate to 200mg**</td>
<td>ORAL</td>
<td>Once daily at night</td>
<td></td>
</tr>
<tr>
<td>1 to 4, &amp; 8 to 11</td>
<td>Dexamethasone</td>
<td>40mg</td>
<td>Oral</td>
<td>Once Daily for 4 days after first of bortezomib each week</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Bortezomib is licensed to be administered by either IV bolus or by subcutaneous (SC) injection. The dose is the same for both routes but they are prepared differently to give a different final strength (see below). Trusts should ensure they have clear protocols in place to avoid potential miss-administration of the sub-cut strength via the IV route and vice versa.

**Thalidomide dose should start at 50mg daily for the first 14 days and then be escalated to 100mg daily for the remaining 14 days of the cycle if well tolerated and then escalated to 200mg daily thereafter.**

### Cycle Length and Number of Days

28 Day cycle, for up to 8 cycles (see note re: treatment review at 4 cycles below). Patients who are eligible for haematopoietic stem cell transplant should receive 4 cycles only.

### Approved Indications

Funded through NHS England Routine Commissioning:

- Induction treatment for previously untreated patients prior to haematopoietic stem cell transplant (NICE TA311)

**Note**

Bortezomib is also approved in other combinations for a number of other indications. Refer to the appropriate protocols for these.
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RECOMMENDED TAKE HOME MEDICATION
GI prophylaxis (Proton Pump Inhibitor) with steroids.

Laxatives may be required if bortezomib causes ileus

Aciclovir 200mg three times a day for the duration of treatment and for 1 month after treatment.

Allopurinol 300mg once daily on the first cycle.

Thrombo-prophylaxis using standard medical prophylaxis dose of Low Molecular Weight Heparin (LMWH) should be prescribed (unless contra-indicated) with all thalidomide-chemotherapy combinations. Duration of LMWH remains uncertain but should be at least for the first 3 months of treatment when the risk of VTE is greatest. LMWH requires dose reduction in renal impairment.

Patients should, normally, also be receiving bisphosphonate therapy (preferably Zoledronic Acid 4mg intravenously).

INVESTIGATIONS / MONITORING REQUIRED
Prior to first cycle: FBC, U&E’s, LFT’s, Calcium, Para Proteins

Prior to each cycle: U&E’s, LFT’s, FBC, Calcium, Para Proteins

ASSESSMENT OF RESPONSE
Patients must be assessed after 4 cycles. If a patient has achieved at least a partial response by cycle 4 they can receive up to a maximum of 6 cycles.

REVIEW BY CLINICIAN
Prior to each cycle (unless being reviewed by a nurse / pharmacist – see below)

NURSE / PHARMACIST LED REVIEW
Nurse or pharmacist led review, within a locally agreed protocol, is acceptable on days 4, 8 and 11. Additionally non-medical review on day 1 for all cycles except the first, and 4th cycle is acceptable within a locally agreed framework.

ADMINISTRATION NOTES
- Bortezomib is rapidly metabolised in the plasma. In order to achieve sufficient intracellular levels of bortezomib, when given intra-venously the injection must be administered very rapidly (over 3-5 seconds). This should be followed immediately by a flush with Sodium Chloride 0.9%. (This is not a concern with sub-cutaneous administration)
- If it is necessary to re-arrange doses of bortezomib to suit bank holidays etc – 72 hours must pass between doses.
- Concomitant use with other medication that causes peripheral neuropathy should be avoided (if possible)
- Consider withholding anti-hypertensives on the morning prior to administration of bortezomib.
- CYP3A4 inhibitors (eg. ketoconazole, ritonavir) may have significant effects on the metabolism of bortezomib.
- Patients with diabetes should increase their monitoring of blood glucose. High dose
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dexamethasone may affect glucose tolerance, however some studies have suggested bortezomib may also cause hypoglycaemia for some patients on oral anti-hyperglycaemic agents

- There have been cases of accidental spinal injection of bortezomib which has been fatal. **Bortezomib must only be given intra-venously or sub-cutaneously.**
- Administer as a subcutaneous injection use the abdomen or thighs as sites for subcutaneous injections, rotate injection sites and administer new injections at least 1 inch from an old site and never into areas where the skin is tender, bruised, erythematous, or indurated. Record injection site.
- Patients **must not** become or attempt to become pregnant during thalidomide treatment. For women of child bearing potential, a negative pregnancy test during the 24 hours prior to each cycle of thalidomide will be required.
- Celgene supply a resource pack to accompany their risk management programme for ThalidomideCelgene™ – this should be referred to for detail.
- Prescriptions must be accompanied by consent form on first cycle. Prescriptions must be accompanied by (or incorporate this in the prescription) a prescription authorisation form on each cycle.
- Thalidomide is sedating and so should be taken at night.
- Dexamethasone dose will normally require administration of 20 tablets, which some patients may find difficult to take at one time. The dose can be divided but the last dose should not be taken after 4pm to avoid insomnia.
- Thalidomide may cause venous thromboembolism – patients should be encouraged to report calf pain early.

**TOXICITIES**
**Common:** Peripheral Neuropathy, Orthostatic/postural hypotension, nausea/vomiting, diarrhea or constipation, thrombocytopenia, neutropenia, fatigue, weakness, diplopia (blurred vision).

**DOSE MODIFICATION / TREATMENT DELAYS**

**Haematological Toxicity:**

Delay treatment on Day 1, 4, 8 or 11 if ANC <0.5 x 10^9 cells/l or PLT <25 x 10^9 cells/l (Grade IV Haematological Toxicity). Restart treatment when toxicity has resolved with a 25% dose reduction.

**Non-Haematological Toxicity:**
**Peripheral Neuropathy:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pain</th>
<th>Definition</th>
<th>Action required</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>No</td>
<td>Paraesthesia and/or loss of reflexes without loss of function</td>
<td>No action required</td>
</tr>
<tr>
<td>I</td>
<td>Yes</td>
<td>Paraesthesia and/or loss of reflexes without loss of function</td>
<td>Reduce dose to 1mg/m²</td>
</tr>
<tr>
<td>II</td>
<td>No</td>
<td>Paraesthesia and/or loss of reflexes interfering with function but not affecting activities of daily living</td>
<td></td>
</tr>
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<table>
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<tr>
<th>Grade</th>
<th>Indicator</th>
<th>Action</th>
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<tr>
<td>II</td>
<td>Yes</td>
<td>Paraesthesia and/or loss of reflexes interfering with function but not affecting activities of daily living</td>
</tr>
<tr>
<td>III</td>
<td>Yes or No</td>
<td>Paraesthesia and/or loss of reflexes interfering with function affecting activities of daily living</td>
</tr>
<tr>
<td>IV</td>
<td>Yes or No</td>
<td>Permanent Sensory Loss that interferes with function</td>
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Other Non-Haematological Toxicity: Delay treatment for any Grade III toxicity. Delay until symptoms resolve to at least Grade II and restart with a 25% dose reduction.

If symptoms recur at the lower dose the risk versus benefits should be considered to make a determination about further dose reduction or discontinuation of therapy.

Renal Function:
The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance (CrCl) >20 ml/min/1.73 m²); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCl <20 ml/min/1.73 m²). Most centres do not make any dose modifications for bortezomib in this situation and monitor for toxicity and adjust accordingly.

Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after dialysis.

Hepatic Function:
Clearance may be affected in patients with hepatic impairment where liver function is impaired. Where bilirubin is > 1.5 x ULN it is recommended to reduce the starting dose of bortezomib to 0.7 mg/m² in the first treatment cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.

TREATMENT LOCATION
Suitable for administration in chemotherapy day units, under the supervision of haematology teams from Level 1 – 4 Haematology Services.

REFERENCES:
- [http://www.velcade-subcut.co.uk/home.html](http://www.velcade-subcut.co.uk/home.html)
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