Indication: Relapsed Multiple Myeloma

Regimen details:
- Lenalidomide 25 mg od orally Days 1 to 21
- Dexamethasone 20mg od orally Days 1, 8, 15, 22
- Cyclophosphamide 500mg od orally Days 1, 8, 15

Administration: Orally

Premedication: Not required

Frequency: 28 day cycle

Extravasation: Not applicable

Anti-emetics: Mild emetogenicity, e.g. metoclopramide 20mg tds prn

Supportive medication:
- Thromboprophylaxis: All patients should receive thromboprophylaxis with aspirin 75mg od unless contraindicated. Patients with a previous VTE or who are at high risk of VTE (one other risk factor in addition to multiple myeloma) should receive LMWH e.g. enoxaparin 40mg sc od as per local protocol.
  - Allopurinol 100 - 300mg od (dependent on renal function). Continued until plateau
  - Antifungal prophylaxis as per local protocol
  - PPI or H2-receptor antagonist

Regular investigations:
- FBC D1
- LFTs D1
- U&Es D1
- Bone profile D1
- Serum paraprotein / serum free light chains at the start of each cycle (as appropriate to myeloma subtype)
- Test for proteinurea before commencing treatment

For women of child bearing potential, pregnancy test within 3 days of the prescription date of every cycle.
Dose Modifications

Haematological Toxicity

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the first cycle will go ahead even if neutrophils <1.0 x 10⁹/L and / or platelets < 30 x 10⁹/L. This should be confirmed with a Consultant

<table>
<thead>
<tr>
<th>Platelets (x 10⁹/L)</th>
<th>Neutrophils (x 10⁹/L)</th>
<th>Lenalidomide and cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 x 10⁹/L &amp; ≥ 1.0 x 10⁹/L</td>
<td>100% dose</td>
<td></td>
</tr>
<tr>
<td>30 - 50 x 10⁹/L or &lt; 1.0 x 10⁹/L</td>
<td>Continue lenalidomide 100% dose and delay cyclophosphamide until platelets ≥ 50 x 10⁹/L and neutrophils ≥ 1.0 x 10⁹/L. Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if platelets &lt; 50 x 10⁹/L and neutrophils &lt; 1.0 x 10⁹/L on day 1 of subsequent cycles (when previously &gt; than these levels), delay cyclophosphamide and consider dose reduction of cyclophosphamide. If the patient was receiving 500mg weekly, reduce to 400mg, if 400mg reduce to 300mg, if 300mg reduce to 200mg NB. Discuss with consultant if thrombocytopenia and /or neutropenia may be related to disease.</td>
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<tr>
<td>&lt; 30 x 10⁹/L or &lt; 0.5 x 10⁹/L</td>
<td>Delay lenalidomide (in addition to cyclophosphamide) until platelets ≥ 30 x 10⁹/L and neutrophils ≥ 0.5 x 10⁹/L. See notes below. NB. Discuss with consultant if thrombocytopenia and /or neutropenia may be related to disease.</td>
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</tbody>
</table>
Notes on lenalidomide dose reductions for haematological toxicity:

<table>
<thead>
<tr>
<th>Dose of lenalidomide patient is taking when haematological toxicity occurs (once daily)</th>
<th>Platelets</th>
<th>Neutrophils</th>
<th>Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>25mg &gt; 30 x 10⁹/L &amp; &lt; 0.5 x 10⁹/L</td>
<td>If the treatment is delayed for the first time due to neutrophils &lt; 0.5 x 10⁹/L only, interrupt treatment and restart when neutrophils &gt; 0.5 x 10⁹/L at 25mg od. If the treatment is delayed for the second time due to neutrophils &lt; 0.5 x 10⁹/L only, interrupt treatment and restart when neutrophils &gt; 0.5 x 10⁹/L at 15mg od.</td>
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<td></td>
</tr>
<tr>
<td>25mg &lt; 30 x 10⁹/L</td>
<td>Interrupt treatment and restart lenalidomide at 15mg od when platelets &gt;30 x 10⁹/L.</td>
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<td></td>
</tr>
<tr>
<td>15mg &lt; 30 x 10⁹/L &amp;/or &lt; 0.5 x 10⁹/L</td>
<td>If the treatment is delayed for a second time due to platelets &lt; 30 x 10⁹/L interrupt treatment and restart at 10mg od when platelets &gt;30 x 10⁹/L. If the treatment is delayed for the third time due to neutrophils &lt; 0.5 x 10⁹/L only, interrupt treatment and restart when neutrophils &gt; 0.5 x 10⁹/L at 10mg od.</td>
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<tr>
<td>10mg</td>
<td>If the treatment is delayed for a third time due to platelets &lt; 30 x 10⁹/L interrupt treatment and restart at 5mg od when platelets &gt;30 x 10⁹/L. If the treatment is delayed for the fourth time due to neutrophils &lt; 0.5 x 10⁹/L only, interrupt treatment and restart when neutrophils &gt; 0.5 x 10⁹/L at 5mg od.</td>
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<tr>
<td>5mg</td>
<td>Do not dose below 5mg once daily.</td>
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</tbody>
</table>

Consideration should be given to GCSF support on days 22, 23, 24 for haematological toxicity. This must be on the recommendation of a Consultant Haematologist.
Renal Impairment

**Lenalidomide**

Lenalidomide should be used with caution in patients with renal impairment. The following dose reductions are recommended by Celgene:

<table>
<thead>
<tr>
<th>Renal function (CrCl ml/min)</th>
<th>Dose of lenalidomide</th>
<th>Dose of cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 ml/min</td>
<td>100% dose</td>
<td>100% dose</td>
</tr>
<tr>
<td>30 - 50 ml/min</td>
<td>10mg once daily.</td>
<td>Consider 25% dose reduction. Dose reduction should be a clinical decision depending on inter-patient variation.</td>
</tr>
<tr>
<td></td>
<td>The dose may be increased to 15mg once daily after 2 cycles if the patient is not responding and is tolerating treatment.</td>
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</tr>
<tr>
<td>10 - 30 ml/min, not requiring dialysis</td>
<td>15mg alternate days. The dose may be increased to 10mg once daily if the patient is tolerating treatment.</td>
<td>Consider 25% dose reduction. Dose reduction should be a clinical decision depending on inter-patient variation.</td>
</tr>
<tr>
<td>End stage renal disease, 10-30 ml/min, requiring dialysis</td>
<td>5mg once daily. On dialysis days, the dose should be administered following dialysis.</td>
<td>Consider 50% dose reduction. On dialysis days, the dose should be administered at least 12 hours prior to dialysis.</td>
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</table>

**Hepatic Impairment**

There is very limited information available regarding the use of lenalidomide in patients with hepatic insufficiency and it should therefore be used with caution.

**Non-Haematological toxicities**

**Lenalidomide:**

Due to the potential for teratogenicity all women of child bearing potential are required to ensure adequate contraception, including a barrier method, is used. Additionally a negative pregnancy test is required prior to commencing each cycle of therapy. Men are required to undertake to use a barrier method of contraception. Peripheral neuropathy, tumour lysis syndrome, hypothyroidism, fatigue, asthenia, constipation, diarrhoea, peripheral oedema, muscle cramp and rash. An increased incidence of venous thrombosis has been reported for patients receiving lenalidomide in combination with dexamethasone and erythropoietin and/or anthracycline chemotherapy regimens

**Dexamethasone** related toxicities including mood changes, restlessness, withdrawal effects, glucose intolerance.

**Cyclophosphamide** related toxicities include: leucopenia, amenorrhoea, haematuria, hair loss, mucosal ulceration, anorexia, nausea and vomiting, pigmentation (typically affecting the palms and nails of the palms and the soles of the feet) and interstitial pulmonary fibrosis.

**Doses reduced for toxicity should not be re-escalated**
Drug interactions: Lenalidomide may increase the plasma levels of digoxin therefore monitoring of the digoxin concentration is advised.

Toxicities: Thrombosis, neutropenia, thrombocytopenia, neuropathy, dry skin.
Steroid related toxicities including mood changes, restlessness, withdrawal effects, glucose intolerance

Comments: Lenalidomide must only be prescribed according to the Revlimid Pregnancy Prevention Programme.
All patients receiving lenalidomide are required to sign a form to confirm that they understand the requirements of the programme.