INDICATIONS

Relapsed multiple myeloma where other treatments are contraindicated or inappropriate. Not licensed for this indication. Funding from Cancer Drugs Fund will be required.

Bendamustine is licensed for first line treatment of myeloma.

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
   - Serum free light chain assay (Freelite)
   - β₂ microglobulin
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions. Samples should be sent to Wessex Regional Genetics Laboratory (address below).
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions. Ensure irradiation card is attached to the patient's notes.
   - Imaging as per NICE/network guidance and clinical presentation.
   - Bone marrow aspirate and trephine (and immunophenotype if appropriate).

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ
ADDITIONAL INVESTIGATIONS:
- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

2. Hydration fluid intake of at least 3 litres/day should be attempted.
3. Fertility - all patients should be offered fertility advice, as appropriate.
4. Counselling- all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
5. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent for the treatment including signing Celgene risk management programme forms (see web page for links).
7. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE-ASSESSMENT
The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Administration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>100 mg po (preferably nocte) Start with 50 mg and escalate if tolerated</td>
<td>Daily</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>60 mg/m² intravenous infusion in 500 ml 0.9% sodium chloride over 30 – 60 min</td>
<td>Days 1, 8</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg po OD</td>
<td>Days 1 – 4, 15 – 18</td>
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</tbody>
</table>

CYCLE FREQUENCY
The cycle is repeated every 28 days for a minimum of 4 cycles and a maximum of 6 cycles depending on response.
DOSE MODIFICATIONS

Neuropathy: Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 and above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap. Subsequent cautious dose escalation should be considered if symptoms permit.

Bendamustine:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10 ml/min – no dose adjustment</td>
<td>Bili 20.4 – 51 70% dose</td>
</tr>
<tr>
<td>≤ 10 ml/min – limited data</td>
<td>Bili &gt; 51 Contraindicated</td>
</tr>
</tbody>
</table>

Myelosuppression: Dose reductions in bendamustine may be necessary. Treatment-related fall in neutrophil count below 1.0 x 10⁹/L or platelets below 75 x 10⁹/L, bendamustine should be temporarily withheld until counts recover with G-CSF therapy + transfusions. If the cytopenias are disease related, please use G-CSF cover and platelet support.

Venous thromboembolism (VTE): There is an increased risk of thrombosis, and some form of prophylaxis is recommended as follows:

1. Aspirin can be appropriate for patients with no additional risk factors for thrombosis

If additional risk factors consider:

2. Prophylactic low-molecular weight heparin OR
3. Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3

Additionally:

4. Can consider use of a direct oral anticoagulant eg apixaban for thromboprophylaxis or treatment dose as indicated.

Aspirin is generally not preferred for higher risk patients with additional risk factors such as immobility. If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.
INVESTIGATIONS – during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca++, glucose – every 3 - 4 weeks.
- Ig’s, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/ blood sugar

CONCURRENT MEDICATIONS

- Skin rash has been reported in patients taking concomitant Allopurinol and Bendamustine
- Consider starting Allopurinol 300 mg daily for 6 days, from day 2 – 7 of first cycle only.
- Prescribe prophylactic laxatives to be taken if needed.
- Proton pump inhibitor or H2 antagonist at clinician’s discretion.
- Prophylactic fluconazole
- Bone protection as per NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation – see above.
- Prophylactic Acyclovir 200 mg bd-tid (depending on renal function)
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft.

EMETIC RISK

Moderate emetic risk on weekly bendamustine days, otherwise minimal or low risk.

ADVERSE EVENTS/ REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic**: A risk management programme should be observed. The concomitant use of 2 effective methods of contraception is mandatory in all female patients of child bearing potential. Male patients should also use a condom when having sexual intercourse with women of child bearing potential. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.
- **Drowsiness, somnolence and sedation**: Take the dose at night time. Thalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking thalidomide.
- **Peripheral neuropathy**: Patients should be advised to report prickling, numbness and paraesthesia.
- **Dizziness and orthostatic hypotension**: Patients should be advised that thalidomide may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position.
- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
- **Other warnings**: Patients should be informed not to donate blood or semen during or within 8
weeks of stopping thalidomide treatment.

- **Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis** have been reported in patients who received bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious mucocutaneous reaction, treatment with bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

**REFERENCES**


3. eMC UK Summary of Product Characteristics for Thalidomide, Celgene, December 2015


## REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Nadjoua Maouche Pharmacist</td>
<td>Formatting, adverse effects and pre assessment section, dose modification, contraindication section removed</td>
<td>May 2016</td>
<td>2.3</td>
<td>May 2018</td>
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<tr>
<td>Dr J. Kothari Consultant</td>
<td>VTE reviewed and regimen specific pre assessment section included</td>
<td>May 2016</td>
<td>2.3</td>
<td>May 2018</td>
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<tr>
<td>Manuela Sultanova Service Coordinator</td>
<td>Formatting, standardisation of some sentences across all protocols e.g pre assessment section, VTE etc.</td>
<td>July 2017</td>
<td>2.4</td>
<td>May 2018</td>
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