Bortezomib, Thalidomide and Dexamethasone (VTD) Induction Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib, thalidomide and dexamethasone for induction treatment of</td>
<td>C90</td>
<td>00274a</td>
<td>Bortezomib Hospital Thalidomide CDS</td>
</tr>
<tr>
<td>adult patients with previously untreated multiple myeloma who are</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>eligible for high-dose chemotherapy with haematopoietic stem cell</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>transplantation</td>
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</tbody>
</table>

If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Bortezomib is administered twice weekly for two weeks on days 1, 4, 8 and 11, dexamethasone on days 1-4 and 9-12 and thalidomide daily in a 21 day treatment cycle for four treatment cycles prior to ASCT or until disease progression or unacceptable toxicity occurs.

It is recommended that patients with at least partial response receive 2 additional cycles.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4, 8 and 11</td>
<td>Bortezomib</td>
<td>1.3mg/m²</td>
<td>SC (abdomen or thigh)</td>
<td>Every 21 days for up to 4 cycles</td>
</tr>
<tr>
<td>1, 2, 3, 4, 9,10,11,12</td>
<td>Dexamethasone</td>
<td>40mg once daily</td>
<td>PO</td>
<td>Every 21 days for up to 4 cycles</td>
</tr>
<tr>
<td>1-21</td>
<td>Thalidomide</td>
<td>100mg</td>
<td>PO</td>
<td>Every 21 days for up to 4 cycles</td>
</tr>
</tbody>
</table>

*Note: In individual cases where approved by Consultant bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route.

*The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered sc or a switch to intravenous injection is recommended.

*Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

*Patients may be started at a dose of thalidomide 50mg at the discretion of the prescribing consultant

At least 72 hours should elapse between consecutive doses of bortezomib.

Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
NCCP Chemotherapy Regimen

- Women of childbearing potential unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met

**PRESCRIPTIVE AUTHORITY:**
The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

**TESTS:**

**Baseline tests:**
- FBC, renal, liver and bone profile
- Uric acid
- Clotting screen
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Assessment of peripheral neuropathy status.
- Assessment and registration as per Thalidomide Pregnancy Prevention Program for both male and female patients.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV

**Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with Lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards (Refer to local policy). Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

**Regular tests:**
- FBC; monitor platelet count at a minimum of day 1 and day 11 each cycle
- Renal, liver and bone profile prior to each cycle.
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Pregnancy test every 28 days if female of childbearing potential.

**Disease monitoring:**
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

**DOSE MODIFICATIONS:**
- Any dose modification should be discussed with a Consultant
Renal and Hepatic impairment:

**Table 1: Dose modifications in patients with renal or hepatic impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Grade of Hepatic Impairment*</th>
<th>Bilirubin Level</th>
<th>SGOT (AST) levels</th>
<th>Modification of starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td><em>It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL &lt; 20ml/min). Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure</em></td>
<td>Mild</td>
<td>≤1 x ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1 - 1.5 x ULN</td>
<td>&gt; ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.5 - 3 x ULN</td>
<td>Any</td>
<td></td>
<td>Reduce dose to 0.7mg/m² in the first treatment cycle. Consider dose escalation to 1mg/m² or further dose reduction to 0.5mg/m² in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3 x ULN</td>
<td>Any</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>No specific dose recommendations</td>
<td>No specific dose recommendations. Monitor patients with severe hepatic impairment closely for adverse reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Neuropathic pain and/or peripheral neuropathy:

**Table 2: Recommended dose modifications for bortezomib-related neuropathy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Severity of neuropathy</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))</td>
<td>Reduce dose to 1 mg/m² or Change treatment schedule to 1.3mg/m² once every week</td>
</tr>
<tr>
<td></td>
<td>Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m² once every week</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Grade 2</td>
<td>Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

Grading based on NCI Common Toxicity Criteria CTCAE v 4.0
Dose reductions for other toxicities:

Table 3: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 Haematological toxicity (ANC &lt; 0.5 x10⁹/L)</td>
<td></td>
<td>withholding bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one dose level reduction from 1.3mg/m² to 1mg/m² or from 1mg/m² to 0.7mg/m². If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.</td>
</tr>
<tr>
<td>Grade ≥ 3 Non-haematological toxicity</td>
<td></td>
<td>withhold bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one dose level reduction from 1.3mg/m² to 1mg/m² or from 1mg/m² to 0.7mg/m². If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.</td>
</tr>
<tr>
<td>Skin rash</td>
<td></td>
<td>withhold treatment and evaluate clinically. If allergic reaction do not resume treatment.</td>
</tr>
<tr>
<td>New or worsening pulmonary symptoms (e.g. cough, dyspnoea)</td>
<td></td>
<td>withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.</td>
</tr>
<tr>
<td>Posterior Reversible Encephalopathy Syndrome (PRES)</td>
<td>Discontinue</td>
<td>withhold treatment. Start standard anticoagulant therapy. Once stabilised on the anticoagulant therapy and complications of thromboembolic event have been managed, thalidomide treatment may be restarted at the original dose dependant on a benefit/risk assessment. Anticoagulant therapy should be continued during the course of thalidomide treatment.</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Discontinue</td>
<td>withhold treatment. Consider PJP prophylaxis (Refer to local policy).</td>
</tr>
<tr>
<td>Thromboembolic Event</td>
<td></td>
<td>withhold treatment and start standard anticoagulant therapy. Once stabilised on the anticoagulant therapy and complications of thromboembolic event have been managed, thalidomide treatment may be restarted at the original dose dependant on a benefit/risk assessment. Anticoagulant therapy should be continued during the course of thalidomide treatment.</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Low (Refer to local policy).

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment.

OTHER SUPPORTIVE CARE:
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H₂ antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy (Refer to local policy).
- Tumour Lysis Syndrome prophylaxis (Refer to local policy).
- Antiviral prophylaxis (Refer to local policy).
- Consider PJP prophylaxis (Refer to local policy).
- Prophylactic laxatives to prevent thalidomide induced constipation(Refer to local policy).
- Thromboprophylaxis (Refer to local policy).

NCCP Regimen: Bortezomib Thalidomide and Dexamethasone (VTD) Induction Therapy

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Version number: 2

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer.

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haematological toxicity**: Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25,000/microliter. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.

- **Progressive multifocal leukoencephalopathy (PML)**: Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PM is suspected patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.

- **Peripheral Neuropathy**: Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

- **Seizures**: Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.

- **Posterior Reversible Encephalopathy Syndrome (PRES)**: In patients developing PRES, treatment with bortezomib should be discontinued.

- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.

- **Renal Impairment**: Patients with renal impairment should be monitored closely.

- **Hepatic Impairment**: Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.

- **Tumour Lysis Syndrome**: Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

- **Teratogenic effects**: Thalidomide must never be used by women who are pregnancy or by women who could become pregnant unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met. These conditions must be fulfilled for all male and female patients.

- **Venous and arterial thromboembolic events**: There is an increased risk of venous and arterial thromboembolism in patients treated with thalidomide particularly during the first 5 months of therapy. Previous history of thromboembolic events may also increase thromboembolic risk in these patients. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.

- **Somnolence**: Patients should be monitored and dose reduction may be required.
DRUG INTERACTIONS:

- Additive hypotensive effect with antihypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia 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 antidiabetics.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- Thalidomide may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 antihistamines, opiate derivatives, barbiturates and alcohol.
- Due to thalidomide’s potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
- Current drug interaction databases should be consulted for more information.

ATC CODE:
- Bortezomib - L01XX32
- Thalidomide - L04AX02

REFERENCES:


Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 This is an unlicensed indication for the use of Bortezomib® in Ireland. Patient’s should be informed of this and consented to treatment in line with the hospital’s policy on the use of unlicensed medication and unlicensed or “off label” indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or “off label” indication has been acknowledged by the hospital’s Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

ii ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/