CyBorD/ Cyclophosphamide, Bortezomib, and Dexamethasone-21 day Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of newly diagnosed symptomatic multiple myeloma&lt;sup&gt;1&lt;/sup&gt;</td>
<td>C90</td>
<td>00273a</td>
</tr>
<tr>
<td>Treatment of relapsed/refractory multiple myeloma&lt;sup&gt;1&lt;/sup&gt;</td>
<td>C90</td>
<td>00273b</td>
</tr>
</tbody>
</table>

ELIGIBILITY:
- Indications as above
- ECOG 0-2
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy.

EXCLUSIONS:
- Hypersensitivity to bortezomib, boron, cyclophosphamide or any of the excipients

TESTS:
**Baseline tests:**
- FBC, Renal, Liver and Bone profile
- Blood pressure.
- *Blood glucose if being treated with oral hypoglycaemics (*See Drug Interactions).
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) and C, HIV

**Regular tests:**
- FBC to be done minimum of day 1 and day 8 of each cycle
- U&Es, LFTs, blood pressure weekly.
NCCP Chemotherapy Protocol

- Blood glucose if being treated with oral hypoglycaemics. (*See Drug Interactions).
- Assessment of peripheral neuropathy status

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.

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.

Treatment consists of four 3-week cycles of bortezomib administered on days 1, 4, 8, and 11; 40 mg dexamethasone* on days 1, 4, 8, and 11; plus cyclophosphamide administered orally on days 1, 8, and 15 or until disease progression or unacceptable toxicity occurs.

*The dexamethasone dose may alternatively be administered as 20 mg on the day of and day after bortezomib (days 1, 2, 4, 5, 8, 9, 11 and 12) as per Kropff et al. 2007

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4, 8, 11</td>
<td>Bortezomib</td>
<td>1.3mg/m²</td>
<td>SC (abdomen or thigh)</td>
</tr>
<tr>
<td>1, 8, 15</td>
<td>Cyclophosphamide</td>
<td>³00mg/m²</td>
<td>PO</td>
</tr>
<tr>
<td>1, 4, 8, 11</td>
<td>Dexamethasone</td>
<td>40mg</td>
<td>PO</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.

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.

Cyclophosphamide is available as 50mg tablets. They should be swallowed with sufficient fluid without chewing. The tablets should not be divided before use.

³Higher doses up to 500mg/m² of cyclophosphamide may be used (Kumar et al)

³Dexamethasone dose may alternatively be administered as 20 mg on the day of and day after bortezomib (days 1, 2, 4, 5, 8, 9, 11 and 12) as per Kropff et al. 2007

Dose reduction of dexamethasone to 20mg or 10mg may be considered in selected patients depending on co-morbidities.
DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

### Haematological toxicities:

#### Table 1: Prior to start of a new cycle

<table>
<thead>
<tr>
<th>ANC (×10^9/L)</th>
<th>Platelets (×10^9/L)</th>
<th>Dose of Bortezomib and Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.5 and ≥ 30</td>
<td></td>
<td>100% Dose</td>
</tr>
<tr>
<td>&lt;0.5 or &lt;30</td>
<td></td>
<td>Consider delay until recovery checking FBC weekly; reduce dose of bortezomib to 1mg/m²</td>
</tr>
</tbody>
</table>

#### Table 2: During a cycle

<table>
<thead>
<tr>
<th>ANC (×10^9/L)</th>
<th>Platelets (×10^9/L)</th>
<th>Dose of Bortezomib and Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 or &lt;30</td>
<td></td>
<td>Omit cyclophosphamide day 15 Withhold treatment with bortezomib until recovery of toxicity. Reinitiate treatment at a reduced dose of bortezomib (1.3 to 1mg/m² or 1mg/m² to 0.7mg/m²) and consider dose reduction of cyclophosphamide</td>
</tr>
</tbody>
</table>

### Hepatic Dysfunction:

#### Table 3. Recommended starting dose modification for bortezomib in patients with hepatic dysfunction

<table>
<thead>
<tr>
<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>Mild</td>
<td>≤1 x ULN</td>
<td>&gt; ULN</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 - 1.5 x ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;1.5 - 3 x ULN</td>
<td>Any</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>Severe</td>
<td>&gt; 3 x ULN</td>
<td>Any</td>
<td>Reduce 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.</td>
</tr>
</tbody>
</table>

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

Table 4: Dose modification of bortezomib and cyclophosphamide in renal impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance ml/min</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Clinical decision-consider whether patient is being treated with high dose treatment</td>
<td></td>
</tr>
</tbody>
</table>

Cyclophosphamide

It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20ml/min). Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure.

Creatinine Clearance ml/min

10-20

< 10

Clinical decision-consider whether patient is being treated with high dose treatment
Neuropathic pain and/or peripheral neuropathy:

Table 5: Recommended dose modifications for bortezomib-related neuropathy

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no loss of function</td>
<td>None</td>
</tr>
<tr>
<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</td>
</tr>
<tr>
<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>Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy</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 6: 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 3 Non-haematological toxicity</td>
<td>Withhold treatment until symptoms of the toxicity have resolved. Treatment may be re-initiated at a 25% reduced dose (1.3mg/m² reduced to 1.0mg.m²; 1.0mg/m² reduced 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>
<td></td>
</tr>
<tr>
<td>New or worsening pulmonary symptoms (e.g. cough, dyspnoea)</td>
<td>Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.</td>
<td></td>
</tr>
<tr>
<td>Posterior Reversible Encephalopathy Syndrome (PRES)</td>
<td>Discontinue bortezomib</td>
<td></td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:
EMETOGENIC POTENTIAL: Low-Moderate (Refer to local policy).

PREMEDICATIONS:
Not usually required.

NCCP Protocol: Bortezomib + Cyclophosphamide + Dexamethasone - 21 day Therapy
Published: 05/04/2017
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Version number: 1

Tumour Group: Myeloma
NCCP Protocol Code: 00273
IHS Contributors:
Dr Patrick Hayden
Dr John Quinn

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Ensure patient remains well hydrated during treatment

**TAKE HOME MEDICATIONS:**
- Oral dexamethasone and cyclophosphamide tablets with instructions on how the tablets should be taken or the appropriate prescriptions for dispensing in a retail pharmacy.
- Low dose antiviral prophylaxis (*Refer to local policy*).
- Consider PJP prophylaxis (*Refer to local policy*).
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- H₂ antagonist or proton pump inhibitor in patients receiving dexamethasone therapy (*Refer to local policy*).
- Tumour Lysis Syndrome prophylaxis (*Refer to local policy*).

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **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.
- **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.
- **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 < 25x10⁹/L. 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.

- **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.
- **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.
- **Steroid use**: Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

**DRUG INTERACTIONS:**

- Additive hypotensive effect with antihypertensives. 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.
- CYP3A inhibitors also decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Current drug interaction databases should be consulted for more information.
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ATC CODE:
Bortezomib - L01XX32
Cyclophosphamide - L01AA01

REIMBURSEMENT CATEGORY:
Bortezomib is funded through local hospital budgets (April 2017).

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

REFERENCES:
1. Reeder et al. Cyclophosphamide, bortezomib and dexamethasone (CyBorD) induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial. Leukaemia 2009; 23(7): 1337–1341

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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/4/2017</td>
<td></td>
<td>Dr Patrick Hayden</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Dr John Quinn</td>
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</tbody>
</table>

1 This is an unlicensed protocol 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.

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