Bortezomib, Melphalan and Prednisolone Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with previously untreated multiple myeloma who are NOT eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.	C90	00275a	Bortezomib; Hospital Melphalan: CDS

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 patients individual clinical circumstances.

Bortezomib is administered subcutaneously in combination with oral melphalan and oral prednisolone as shown in the treatment table below. A 6-week period is considered a treatment cycle.

Treatment is administered for 9 bortezomib treatment cycles or until disease progression or unacceptable toxicity develops.

- In **Cycles 1-4, bortezomib is administered twice weekly** on days 1, 4, 8, 11, 22, 25, 29 and 32.
- **In Cycles 5-9, bortezomib is administered once weekly** on days 1, 8, 22 and 29.
- **Melphalan and prednisone** should both be given orally on **days 1, 2, 3 and 4 of the first week of each cycle.**
- **As an alternative, bortezomib may be given once weekly on days 1, 8, 15 and 22 of a 5 week cycle in select patients at the treating clinican's discretion.**

Day	Drug	Dose	Route	Cycle
1, 4, 8, 11, 22, 25, 29, 32	Bortezomib	1.3 mg/m^2	[ab,]SC (abdomen or thigh)	1-4 (every 6 weeks)
1, 8, 22 and 29	Bortezomib	1.3 mg/m^2	[ab,]SC (abdomen or thigh)	5-9 (every 6 weeks)
1-4	Melphalan	9 mg/m^2	PO	1-9 (every 6 weeks)
1-4	Prednisolone	60 mg/m^2	PO	1-9 (every 6 weeks)
[a]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				
[b]The solution should be injected subcutaneously, at a 45-90^0 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*.** *Here*				

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ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, melphalan or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease

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 (patients on oral hypoglycaemics).
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

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)

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

Haematological:

Prior to initiating a new cycle of therapy

- Platelets ≥70 x 10^9/L and ANC ≥1 x 10^9/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline

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Table 1: Dose reduction steps for bortezomib

Dose Level	Dose
Starting dose	1.3mg/m^2
Dose level 1	1.0mg/m^2
Dose level 2	0.7mg/m^2
Dose level 3	Discontinue

Table 2: Dose modifications for haematological toxicity

Toxicity	Dose Modification
If prolonged Grade 4 Neutropenia (ANC < 0.5 x 10^9/L) or Thrombocytopenia (Platelets < 25 x 10^9/L) or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
If platelet ≤ 30x10^9/L or ANC ≤ 0.75 x 10^9/L on a bortezomib dosing day (other than day 1)	Withhold bortezomib
If several bortezomib doses in a cycle are withheld (≥ 2 doses)	Reduce bortezomib from 1.3mg/m^2 to 1 mg/m^2 or from 1mg/m^2 to 0.7mg/m^2

Renal and Hepatic Impairment:

Table 3: Recommended dose modification for renal or hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="6">Bortezomib</td><td colspan="2" rowspan="6">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</td><td>Grade of Hepatic Impairment*</td><td>Bilirubin Level**</td><td>(AST) Levels**</td><td>Modification of starting dose</td></tr>
<tr><td rowspan="2">Mild</td><td>≤1 x ULN</td><td>> ULN</td><td>None</td></tr>
<tr><td>>1-1.5xULN</td><td>Any</td><td>None</td></tr>
<tr><td>Moderate</td><td>>1.5-3xULN</td><td>Any</td><td rowspan="3">Reduce dose to 0.7mg/m^2 in the first treatment cycle.
Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.</td></tr>
<tr><td>Severe</td><td>>3xULN</td><td>Any</td></tr>
<tr><td></td></tr>
<tr><td rowspan="4">Melphalan</td><td>Creatinine Clearance(ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">No dose changes recommended.
If excessive toxicity, consider dose reduction on subsequent cycles</td></tr>
<tr><td>>50</td><td>100%</td></tr>
<tr><td>10-50</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
</table>

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

**ULN = Upper Limit Normal

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Neuropathic pain and/or peripheral neuropathy:

Table 4: Dose modifications for bortezomib related neuropathy

Severity of neuropathy	Dose Modification
Grade 1	None
Grade 1 with pain or Grade 2	Reduce dose to 1mg/m^2 or Change treatment schedule to 1.3mg/m^2 once every week
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
Grade 4 and/or severe autonomic neuropathy	Discontinue treatment
Grade 1: Asymptomatic; clinical or diagnostic observations only Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living (ADL) Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated *Grading based on NCI Common Toxicity Criteria CTCAE v 4*	

Dose reductions for other toxicities:

Table 5: Dose modification schedule of *bortezomib* based on adverse events

Adverse reactions*	Recommended dose modification
Grade ≥3 Non-haematological toxicity	Withhold bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one dose level reduction from 1.3mg/m^2 to 1 mg/m^2 or from 1mg/m^2 to 0.7mg/m^2
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue bortezomib

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Bortezomib- Low **(Refer to local policy).**
Melphalan – Minimal **(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 H_2 antagonist or proton pump inhibitor **(Refer to local policy).**
- Tumour Lysis Syndrome prophylaxis (Refer to local policy).
- Consider PJP prophylaxis (Refer to local policy)
- Antiviral prophylaxis (Refer to local policy).

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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.

- **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.
- **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 anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

Bortezomib:

- **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 < 25x 10^9cells/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.
- **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.
- **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.

Melphalan

- **Myelosuppression:** Melphalan is a potent myelosuppressive agent.
- **Renal Impairment:** Clearance of melphalan may be reduced in patients with renal impairment who may also have uraemic bone marrow suppression. Dose reduction may therefore be necessary and these patients should be closely observed.
- **Mutagenecity:** Chromosome aberrations have been observed in patients treated with melphalan.
- **Carcinogenecity:** There have been reports of acute leukaemia occurring after melphalan treatment for multiple myeloma.

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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.
- Impaired renal function has been described in bone marrow patients who were pre-conditioned with high dose IV Melphalan and who subsequently received cyclosporine to prevent graft-versus-host disease.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Moreau P, Coiteux V, Hulin C, et al. Prospective Comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. Haematologica 2008;93:1908-11.
2. Chanan-Kahn, Analysis of Herpes zoster events among bortezomib-treated patients. J Clin Oncol. 2008;26:4784- 90
3. San Miguel JF et al. Bortezomib plus Melphalan and Prednisone for initial treatment of Multiple Myeloma. NEJM. 2008;359(9):906-917
4. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, Gentili S, Patriarca F, Nozzoli C, Levi A, Guglielmelli T, Benevolo G, Callea V, Rizzo V, Cangialosi C, Musto P, De Rosa L, Liberati AM, Grasso M, Falcone AP, Evangelista A, Cavo M, Gaidano G, Boccadoro M, Palumbo A. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010 Dec 2;116(23):4745-53. doi: 10.1182/blood-2010-07-294983
5. Mateos MV, Hernández JM, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood. 2006;108(7):2165-72.
6. Mateos MV, Hernández JM, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. Haematologica 2008;93(4):560-5.
7. Mateos MV, Richardson PG et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28(13):2259-66.
8. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. Lancet Oncol. 2011;12(5):431- 40.
9. Richardson PG, Briemberg H et al. Frequency, Characteristics, and Reversibility of Peripheral Neuropathy During Treatment of Advanced Multiple Myeloma With Bortezomib. J Clin Oncol. 2006: 24(19);3113-3120.
10. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf

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11. VELCADE® Summary of Product Characteristics Accessed October 2020 Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf
12. ALKERAN® Summary of Product Characteristics Accessed October 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1691-004-001_14112019130102.pdf
13. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	08/08/2016		Dr John Quinn
2	12/10/2018	Updated with new NCCP regimen template and Hepatitis B recommendations	Dr John Quinn
3	08/03/2021	Regimen review Addition of table for dose reduction steps for bortezomib Updated adverse events/regimen specific complications with regard to management of hepatitis B reactivation	Dr John Quinn

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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