Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) 21-Day Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status*
Treatment of newly diagnosed symptomatic multiple myeloma[i]	C90	00273a	Hospital
Treatment of relapsed/refractory multiple myeloma[i]	C90	00273b	Hospital

**If the reimbursement status[ii] 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 patients individual clinical circumstances.

Treatment consists of four 3-week cycles of bortezomib administered on days 1, 4, 8, and 11; dexamethasone 40 mg* 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 1 Regimen Treatment Table

Day	Drug	Dose	Route
1 , 4, 8, 11	Bortezomib	1.3mg/m^2	[a,b] SC (abdomen or thigh)
1, 8, 15	Cyclophosphamide	[C]300mg/m^2	PO
1 , 4, 8, 11	[d]Dexamethasone	40mg	PO[D], Take in the morning with food
[a] 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° 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 IV 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			
[C] Cyclophosphamide is available as 50mg tablets. They should be swallowed with sufficient fluid without chewing. The tablets should not be divided before use. Higher doses up to 500mg/m2 of cyclophosphamide may be used (Kumar et al)			
[D] 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. Dose reduction of dexamethasone to 20mg or 10mg may be considered in selected patients depending on co morbidities.			

ELIGIBILTY:

- 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, dexamethasone or any of the excipients

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.
- Blood pressure.
- Blood glucose* if being treated with oral hypoglycaemics (*See Drug Interactions).
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), hepatitis C, 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 anti-viral therapy, 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 to be done minimum of day 1 and day 8 of each cycle
- Renal, Liver and bone profile
- Blood pressure weekly.
- Assessment of peripheral neuropathy status
- 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 toxicities:

Table 2 Dose Modification of Bortezomib and Cyclophosphamide for Haematological Toxicity

Prior to Starting a new cycle			
ANC (x10^9/L)		**Platelets(x10^9/L)**	**Dose of Bortezomib and Cyclophosphamide**
≥ 0.5	and	≥ 30	100% Dose
<0.5	or	<30	Consider delay until recovery checking FBC weekly; reduce dose of bortezomib to 1mg/m^2 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.
During a cycle			
ANC (x10^9/L)		**Platelets(x10^9/L)**	**Dose of Bortezomib and Cyclophosphamide**
<0.5	or	<30	Omit cyclophosphamide day 15 Withhold treatment with bortezomib until recovery of toxicity. Reinitiate treatment at a reduced dose of bortezomib (1.3 to 1mg/m^2 or 1mg/m^2 to 0.7mg/m^2) and consider dose reduction of cyclophosphamide 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.

Renal impairment:

Table 3 Dose Modification of Bortezomib and Cyclophosphamide in Renal Impairment

Category	**Dose modification**	
Bortezomib	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.	
Cyclophosphamide	**Creatinine Clearance ml/min**	**Dose modification**
	>20	100%
	10-20	75%
	< 10	50%
	Clinical decision-consider whether patient is being treated with high dose treatment	

Hepatic impairment:

Table 4 Dose Modification of Bortezomib in Hepatic Impairment

Grade*	Bilirubin Level	SGOT (AST) levels	Modification of starting dose
Mild	≤1 x ULN	>ULN	None
	>1 - 1.5 x ULN	Any	None
Moderate	>1.5 - 3 x ULN	Any	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.
Severe	> 3 x ULN	Any	Reduce bortezomib to 0.7 mg/m^{2}in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).
SGOT=serum glutamic oxaloacetic transaminase;

Neuropathic pain and/or peripheral neuropathy:

Table 5 Dose modifications for Bortezomib Related Neuropathy

Severity of neuropathy	Dose Modification
Grade 1(asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce dose to 1 mg/m^2
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 6: Dose Modification of Bortezomib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 3 Non-haematological toxicity	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at a 25% reduced dose (1.3mg/m^2 reduced to 1mg/m^2; 1mg/m^2 reduced to 0.7mg/m^2). 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.
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 treatment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low-moderate (**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.
- H_2-antagonist or PPI in patients receiving dexamethasone therapy (**Refer to local policy**).
- Low dose antiviral prophylaxis (**Refer to local policy**).
- Consider PJP prophylaxis (**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 <25 x 10^9/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 anti-hypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of anti-hypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medications.
- 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. Current drug interaction databases should be consulted for more information.
- 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.

ATC CODE:

Bortezomib - L01XX32
Cyclophosphamide - L01AA01

REFERENCES:

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Haematol 2007;138(3):330-337.
3. Kumar S et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma Blood 2012;119:4375-4382.
4. 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.
5. Chanan-Kahn, Analysis of Herpes zoster events among bortezomib-treated patients. J Clin Oncol. 2008;26:4784- 90.
6. 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.
7. VELCADE® Summary of Product Characteristics, EMA, Last updated: 29-Mar-19, Accessed Mar-2019 Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	05/04/2017		Dr Patrick Hayden Dr John Quinn
2	19/06/2019	Updated to new template. Updated recommendation on Hep B reactivation Updated dose modifications for haematological toxicity	Dr Patrick Hayden Dr John Quinn

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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

[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/