Regimen Monograph

A - Regimen Name

BORT Regimen

Bortezomib

Disease Site	Hematologic - Lymphoma - Non-Hodgkin's Low Grade
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Treatment of mantle cell lymphoma in patients who have relapsed or are refractory to at least one prior therapy. Approval was based on data from a large single arm phase II trial.

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B - Drug Regimen

bortezomib	1.3 mg /m²	IV / Subcut	Days 1, 4, 8 and 11

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.
- Consider the use of antiviral prophylaxis against herpes zoster (shingles) during bortezomib therapy.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dose Level	Bortezomib Dose (mg/m^2)
0	1.3
-1	1
-2	0.7

Dexamethasone doses may be reduced for dexamethasone-related adverse events (i.e. hypertension, hyperglycemia, fluid retention) to improve tolerability.

Table A: Dose Modifications for Hematological and Non-Hematological Toxicities:

Toxicity	Grade	Bortezomib Dose
ANC	<0.5 x 10^9/L	Hold+ until recovery; restart at 1 dose level ↓.
Platelets	< 25 x 10^9/L	
Drug-related fluid retention*	Grade 2	Continue at 1 dose level ↓.
	≥ Grade 3	Discontinue.
Non-hematologic toxicity (see table D for neurotoxicity)	≥ Grade 3	Hold+ until ≤ grade 1 or baseline; restart at 1 dose level ↓. Consider discontinuing for grade 4.
Pneumonitis		Hold and investigate; discontinue if confirmed.
PRES/ PML/ or dose-limiting toxicity at 0.7 mg/m^2	Any	Discontinue.

+ If no recovery after delay, discontinue.

*Used in mantle cell lymphoma trial by Belch et al.

Table B: Dosage for Neurotoxicity

Severity of Peripheral Neuropathy	Bortezomib Dosage and Regimen Modification
Grade 1 (paresthesia, weakness and/or loss of reflexes) without pain or loss of function	No action.
Grade 1 with pain or grade 2 (interfering with function but not with activities of daily living)	Restart at 1 dose level ↓.
Grade 2 with pain or grade 3 (interfering with activities of daily living)	Hold until toxicity resolves; restart at 2 dose level ↓ (0.7mg/m^2) and give once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis, and/or severe autonomic neuropathy)	Discontinue.

Hepatic Impairment

Bortezomib is metabolized by liver enzymes and exposure is increased in patients with moderate to severe hepatic impairment. Patients with hepatic impairment should be treated with extreme caution and should be closely monitored for toxicities, and dose reduction should be considered.

Suggested dose modifications:

Bilirubin	AST	Starting Dose
≤ 1 x ULN	> ULN	No change
> 1 – 1.5 x ULN	Any	No change
> 1.5 – 3 x ULN	Any	First cycle: ↓ to 0.7mg/m^2. Subsequent cycles: Consider ↑ dose to 1mg/m^2 or further ↓ dose to 0.5 mg/m^2 based on patient tolerability.
> 3 x ULN	Any	

Renal Impairment

Dose adjustments are not necessary in patients with renal insufficiency.(Dimopolous 2010) Patients with compromised renal function should be monitored carefully when treated with bortezomib, especially if creatinine clearance is less than 30mL/min. Bortezomib should be given after dialysis.

Dosage in the Elderly

No dose adjustment is necessary.

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F - Adverse Effects

Refer to bortezomib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue • Diarrhea • Nausea, vomiting	• Constipation (may be severe) • Neuropathy (may be severe) • Fever • Myelosuppression +/- infection (including opportunistic, viral re-activation), bleeding (may be severe) • Anorexia, weight loss • Headache • Cough, dyspnea (may be severe)	• Musculoskeletal pain • Rash (may be severe) • Insomnia • Edema (may be severe) • Abdominal pain • Dizziness • Abnormal electrolyte(s) (K, Mg, Ca, Na, PO4) • Hypotension (may be severe) • Rigors • Blurred vision • Dyspepsia	• Cardiotoxicity • Arrhythmia • QTc prolongation • Arterial/venous thromboembolism • Pericarditis • Tumour lysis syndrome • Disseminated intravascular coagulation • Hemolytic uremic syndrome • GI obstruction, perforation • Pancreatitis • Hepatotoxicity • Nephrotoxicity • Nephrotic syndrome • Hypersensitivity • Pulmonary hypertension • PML • PRES/PRLS • Optic neuritis • Seizure • Graft loss • Sudden death (with induction)

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G - Interactions

Refer to bortezomib, dexamethasone drug monograph(s) for additional details

- Avoid co-administration with strong CYP3A4 inducers; monitor closely for toxicity if co-administered with CYP3A4 inhibitors.
- Avoid green tea and preparations containing green tea.
- Avoid vitamin C supplementation.
- Exercise caution and monitor blood glucose when co-administered with hypoglycemic agents.
- Exercise caution and monitor with drugs associated with neuropathy or hypotension.

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H - Drug Administration and Special Precautions

Refer to bortezomib drug monograph(s) for additional details

Administration

- Bortezomib may be administered:
  - Intravenously (1 mg/mL concentration) as a 3 to 5 second bolus injection or
  - Subcutaneous (2.5 mg/mL concentration)
- Bortezomib should only be reconstituted with 0.9% sodium chloride injection.
- Bortezomib is FATAL IF GIVEN INTRATHECALLY.
- Bortezomib has a **narrow therapeutic range**. **If a different reconstituted concentration is used for each route of administration, exercise caution when reconstituting and calculating the dose volume.**
- If local injection site reactions occur following subcutaneous bortezomib, consider using a less concentrated solution subcutaneously (1 mg/mL), or administer as IV.
- For subcutaneous use, bortezomib solution is injected into the right or left sides of the thighs or abdomen. Rotate injection sites with subsequent injections. Give new injections at least 2.5 cm from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.
- Unopened vials may be stored between 15 and 30º C. Retain in original package to protect

from light.

Contraindications

- Patients with hypersensitivity to bortezomib, boron, mannitol, or other excipients
- Bortezomib is NOT for intrathecal use. Fatal if given intrathecally.

Warning and Precautions

- Caution should be exercised when driving or using machinery, and in patients on medication(s) that may lead to hypotension, or patients with dehydration or history of syncope, due to the risk of hypotension and dizziness.
- Use with caution in patients with amyloidosis or risk factors for seizures.
- Use with caution in patients with risk factors for or existing cardiac disease.
- Use with caution in patients with pre-existing peripheral or autonomic neuropathy; patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

Pregnancy and Lactation

- Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Adequate contraception should be used by both genders during bortezomib treatment and for 3 months after treatment completion.
- Breastfeeding is not recommended.
- Fertility effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood glucose levels, especially in patients using antidiabetic medications and those receiving dexamethasone; baseline and as clinically indicated

- CBC; Baseline and as clinically indicated; monitor platelets before each dose
- Chest X-ray; baseline, then Chest X-ray and lung function assessment if ILD is suspected
- Liver and renal function tests, electrolytes; baseline, at each cycle and as clinically indicated
- Clinical toxicity assessment of fatigue, hypotension, neurotoxicity, infection, bleeding, respiratory symptoms, tumour lysis syndrome, cardiovascular, skin, neurologic and GI side effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- LVEF monitoring in patients with cardiac risk factors; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	16.369 minutes
Nursing Workload (average time per visit)	27.5 minutes

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K - References

Bortezomib drug monograph, Cancer Care Ontario.

Fisher RL, Bernstein SH, Kahl, BS, et al. Multicenter phase II Study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. JCO 2006: 24(30); 4867-74.

Goy A, Bernstein SH, Kahl, BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Annals of Oncology 2009 Mar;20(3):520-5.

July 2019 Updated monograph format, Adverse Effects, Pregnancy and Lactation and Monitoring sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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