

Regimen Monograph

[Regimen Name](#) | [Drug Regimen](#) | [Cycle Frequency](#) | [Premedication and Supportive Measures](#) | [Dose Modifications](#) | [Adverse Effects](#) | [Interactions](#) | [Drug Administration and Special Precautions](#) | [Recommended Clinical Monitoring](#) | [Administrative Information](#) | [References](#) | [Other Notes](#) | [Disclaimer](#)

A - Regimen Name

BORT(MNT) Regimen

BORT(MNT)

Disease Site Hematologic - Multiple Myeloma

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 For the maintenance treatment of multiple myeloma following autologous stem cell transplant (ASCT). In the clinical trial, patients were eligible for bortezomib maintenance if they previously received bortezomib as part of induction prior to ASCT. Approval was based on an improvement in progression-free survival.

[back to top](#)

B - Drug Regimen

bortezomib	1.3 mg /m ²	Subcut	Day 1
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(This drug is not publicly funded. Universal compassionate access program is available.)

[back to top](#)

C - Cycle Frequency**REPEAT EVERY 14 DAYS**

Starting 3 to 4 months post-ASCT for up to 2 years unless disease progression or unacceptable toxicity occurs

[back to top](#)

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.

[back to top](#)

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	

BORT(MNT)

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	<u>Bortezomib Dosage and Regimen Modification</u>
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.

[back to top](#)

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
<ul style="list-style-type: none"> • Fatigue • Diarrhea • Nausea, vomiting 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Musculoskeletal pain • Rash (may be severe) • Insomnia • Edema (may be severe) • Abdominal pain • Dizziness • Abnormal electrolyte(s) (K, Mg, Ca, Na, PO₄) • Hypotension (may 	<ul style="list-style-type: none"> • Cardiotoxicity • Arrhythmia • QTc prolongation • Arterial/venous thromboembolism • Pericarditis • Tumour lysis syndrome • Disseminated intravascular coagulation • Hemolytic uremic syndrome

	be severe)	be severe) <ul style="list-style-type: none"> • Rigors • Blurred vision • Dyspepsia 	<ul style="list-style-type: none"> • 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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[back to top](#)

G - Interactions

Refer to [bortezomib](#) 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.

[back to top](#)

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 30° C. Retain in original package and 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

[back to top](#)

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 (at minimum, prior to each cycle); 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

[back to top](#)

J - Administrative Information

Approximate Patient Visit 0.5 hour
Pharmacy Workload (average time per visit) 16.369 minutes
Nursing Workload (average time per visit) 27.500 minutes

[back to top](#)

K - References

Bortezomib drug monograph, Cancer Care Ontario.

Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol*. 2012 Aug 20;30(24):2946-55.

PEBC Advice Documents or Guidelines

- [Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline](#)

June 2020 Updated bortezomib (compassionate supply available)

[back to top](#)

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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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[back to top](#)