Drug Monograph

A - Drug Name

bortezomib

COMMON TRADE NAME(S): Velcade®

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B - Mechanism of Action and Pharmacokinetics

Bortezomib is a modified dipeptidyl boronic acid. It is a reversible inhibitor of the 26S proteasome, a large protein complex that degrades ubiquitinated proteins. Inhibition of the proteasome pathway leads to activation of multiple signaling cascades cell-cycle arrest, and apoptosis.

Absorption	Comparable exposure was observed following repeated intravenous or subcutaneous doses.	
Distribution	After IV administration, more than 90% of the drug is rapidly cleared from the plasma within minutes. Distributed widely to peripheral tissues.	
	Cross blood brain barrier?	no
	PPB	83%
Metabolism	Active metabolites	no
	Inactive metabolites	yes

Elimination	Not characterized in humans. Route of elimination appeared to be species-specific.	
	Half-life	Multiple dosing: • 1 mg/m^2: 40 to 193 hours • 1.3 mg/m^2: 49 to 109 hours

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma
- Mantle cell lymphoma

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

The following table contains adverse effects that occurred in ≥10% of patients in single agent intravenous randomized studies in myeloma or were considered severe or life-threatening from other clinical studies or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (rare)	E
Cardiovascular	Arrhythmia (rare)	I E
	Arterial thromboembolism (rare)	E D
	Cardiotoxicity (rare)	E
	Hypotension (11%) (orthostatic)	I E
	Pericarditis (<1%) (rare)	I E
	Pulmonary hypertension (rare)	E
	QT interval prolonged (rare)	I E
	Sudden death (rare, with induction therapy)	
	Venous thromboembolism (rare)	E D
Dermatological	Rash (24%)	I E
Gastrointestinal	Abdominal pain (16%)	I E
	Anorexia, weight loss (34%)	E
	Constipation (42%) (2% severe)	E
	Diarrhea (58%)	I E
	Dyspepsia (10%)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Nausea, vomiting (57%)	I
General	Edema (17%) (including effusions)	E
	Fatigue (61%)	E
	Fever (35%)	E
	Rigors (11%)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Hemolytic uremic syndrome (rare)	E

	Myelosuppression ± infection, bleeding (35%) (including atypical, viral reactivation) (26% severe)	E
Hepatobiliary	↑ LFTs (rare; may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare, may be severe)	I
Immune	Other (Graft loss - rare)	
Injection site	Injection site reaction (6% for SC, rare for IV)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (13%) (K, Mg, Ca, Na, PO4)	E
	Tumour lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (24%)	E
Nervous System	Cognitive disturbance (rare)	E
	Dizziness (14%)	I E
	Headache (26%)	E
	Insomnia (18%)	E
	Leukoencephalopathy (PML - rare)	E
	Neuropathy (36%) (sensory, motor, including Guillan-Barre - rare; autonomic - may be severe)	E
	Optic neuritis (rare)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Seizure (rare)	E
Ophthalmic	Blurred vision (11%)	E
Renal	Nephrotoxicity (rare)	E
	Proteinuria (nephrotic syndrome - rare)	E
Respiratory	Cough, dyspnea (25%)	E
	Pneumonitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for bortezomib include fatigue, diarrhea, nausea, vomiting, constipation, neuropathy, fever, myelosuppression ± infection, bleeding, anorexia, weight loss, headache, cough and dyspnea.

Patients at risk of **tumour lysis syndrome** (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Myelosuppression was more common in the myeloma studies, while **neuropathy** and **rash** were more common in the mantle cell lymphoma studies. Myelosuppression is not cumulative and nadirs usually occur at ± 8-11 days. **Thrombocytopenia** is common, dose-related and more severe in patients with low platelets prior to therapy. Hemorrhage (including GI and CNS) due to low platelet count has been observed.

Bortezomib treatment can cause **nausea, vomiting**, and **diarrhea**, sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration. **Constipation** may occur as well as **ileus**.

Viral reactivation, including herpes zoster, has been reported in up to 14% of patients. Prophylaxis is recommended. Rare cases of JC virus, resulting in fatal p**rogressive multifocal leukoencephalopathy** (PML) have been reported. New onset or worsening neurological symptoms should be referred to a neurologist.

Bortezomib may cause a dose-related and cumulative **peripheral neuropathy** that is predominantly sensory, although severe cases of mixed sensory-motor or motor neuropathy (including Guillain-Barre) have also been reported. The incidence is lower when given subcutaneously. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening during treatment with bortezomib. Subcutaneous bortezomib could be considered. The neuropathy appears reversible in most patients. **Autonomic neuropathy** may occur and may be severe.

Bortezomib treatment can cause orthostatic/postural **hypotension**. Some cases are also associated with syncope. These events can occur throughout therapy and may be more common in patients with pre-existing hypertension.

Hypertension has also been reported, and rarely, patients may present with **posterior reversible leukoencephalopathy syndrome** (PRES) with hypertension, headache and visual loss.

Acute development or exacerbation of congestive **heart failure** and/or new onset of **decreased left ventricular ejection fraction** has been seen, even in patients who do not have risk factors or existing heart disease.

Rare cases of **acute liver failure** have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. There is limited re-challenge information in these patients.

Rare fatal cases of pulmonary disorders including **pneumonitis** have been reported. Patients should be promptly investigated if any new or worsening pulmonary symptoms occur and bortezomib discontinued if pneumonitis is confirmed.

When given subcutaneously, there is a lower incidence of peripheral neuropathy but more hypertension, weight loss, fever and injection site reactions.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline

Bortezomib has a narrow therapeutic index and should be used with caution.

Consider the use of antiviral prophylaxis against herpes zoster (shingles) during bortezomib therapy.

Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Doses should be administered at least 72 hours apart to minimize drug accumulation and missed doses should not be made up.

Bortezomib is used as a single agent (q3w) for relapsed myeloma and for mantle cell lymphoma, and in combination with a standard melphalan and prednisone regimen (q6w) for previously untreated myeloma or medically recognized combination therapy for induction treatment prior to stem cell transplantation.

Adults:

Single Agent in Relapsed Multiple Myeloma or Mantle Cell Lymphoma:

Intravenous / Subcutaneous: 1.3 mg/m² on Days 1, 4, 8, 11; q 3 weeks for up to 8 cycles.

For patients with continuing response after 8 cycles, consider continuation with a q 5 weeks schedule (Day 1, 8, 15, 22, q 5 weeks)

As Part of Induction therapy for Previously Untreated Multiple Myeloma Pre-Stem Cell Transplantation:

Intravenous / Subcutaneous: 1.3 mg/m² Days 1, 4, 8, 11; q 3 weeks for 3-6 cycles (Although not approved by Health Canada, some clinical trials have used bortezomib 1.5 mg/m^2 IV weekly on Days 1, 8, 15, and 22; q 4 weeks)

With Melphalan and Prednisone, in Multiple Myeloma Patients Unsuitable for Stem Cell Transplantation:

Intravenous / Subcutaneous:
Cycles 1-4 - 1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29, 32; q 6 weeks
Cycles 5-9 - 1.3 mg/m^2 on Days 1, 8, 22, 29; q 6 weeks

(Refer to BMP regimen monograph)

As part of combination therapy (bortezomib-rituximab-cyclophosphamide-doxorubicin-prednisone) in Previously Untreated Mantle Cell Lymphoma:

Intravenous / Subcutaneous: 1.3 mg/m² on days 1, 4, 8, 11; q 3 weeks for 6 cycles (2 additional cycles may be given if the first response is documented at cycle 6)

With

Day 1: rituximab 375 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV;

Days 1-5: prednisone 100 mg/m^2 PO

Dosage with Toxicity:

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

Patients with symptoms of pneumonitis or ARDS should have treatment withheld and be appropriately investigated.

Table A:

- Single Agent for Relapsed/Refractory Myeloma or Mantle Cell Lymphoma
- As Part of Induction therapy for Previously Untreated transplant eligible Multiple Myeloma (i.e.CYBORD)

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:

- Previously untreated transplant ineligible multiple myeloma (In Combination with Melphalan and Prednisone)

Toxicity in Previous Cycle / Toxicity Day 1 of Cycle	**Dose Modification and Action**
Day 1 ANC < 1 x 10^9/L or platelets < 70 x 10^9/L	Delay until recovery.
Prolonged (≥ 5 days) grade 4 ANC or platelets or febrile neutropenia or thrombocytopenic bleeding in previous cycle	Consider ↓ melphalan dose by 25%.
Bortezomib held (≥ 3 times in a cycle during twice weekly administration, or ≥ 2 times in a cycle during weekly administration)	↓ bortezomib by 1 dose level.
Grade 3 or 4 non-hematologic toxicity (see table D for neurotoxicity)	Hold until ≤ grade 1/baseline; restart with 1 dose level ↓. Consider discontinuing for grade 4.
Pneumonitis	Hold and investigate; discontinue if confirmed.
Any grade PRES/ PML/ or dose-limiting toxicity at 0.7 mg/m^2	Discontinue.
Toxicity Within Cycle	
ANC ≤ 0.75 x 10^9/L or platelet ≤ 30 x 10^9/L	Hold both bortezomib and melphalan (if applicable).
Grade 3 or 4 non-hematologic toxicity (see table D for neurotoxicity)	Hold until ≤ grade 1/baseline; restart with 1 dose level ↓. Consider discontinuing for grade 4.
Pneumonitis	Hold and investigate; discontinue if confirmed.
Any grade PRES/ PML/ or dose-limiting toxicity at 0.7 mg/m^2	Discontinue.

Table C:

- Previously Untreated Mantle Cell Lymphoma (in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone)

Toxicity Prior Cycle	**Bortezomib Dose Modification and Action**
≥ Grade 3 neutropenia with fever, grade 4 neutropenia lasting more than 7 days, or a platelet count < 10 × 10^9/L	Delay until recovery. Hold for up to 2 weeks until the patient has an ANC ≥ 0.75 × 10^9/L and a platelet count ≥ 25 × 10^9/L; restart at 1 dose level ↓. Discontinue if no recovery within 2 weeks.
Grade 3 or 4 non-hematologic toxicity (see table D for neurotoxicity)	Hold until recovery to ≥ grade 2; restart at 1 dose level ↓. Consider discontinuing for grade 4 toxicity.
Day 1 of Cycle: Do not start until platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, hemoglobin ≥ 80 g/L and other toxicities ≤ grade 1.	
If platelet counts < 100 × 10^9/L. or ANC < 1.5 × 10^9/L and hemoglobin < 80 g/L	Delay until recovery.
Grade 3 or 4 non-hematologic toxicity (see table D for neurotoxicity)	Hold until recovery to ≥ grade 2; restart at 1 dose level ↓. Consider discontinuing for grade 4 toxicity.
Toxicity Within Cycle	
If platelet counts < 25 × 10^9/L or ANC < 0.75 × 10^9/L	Hold bortezomib for up to 2 days (ensure at least 72 hours elapse after this dose until Day 8 or Day 11). If cannot be given within 2 days, skip dose and do not make up later in the cycle.
≥ Grade 3 neutropenia with fever, grade 4 neutropenia lasting more than 7 days, or a platelet count < 10 × 10^9/L	Delay until recovery. Hold for up to 2 weeks until the patient has an ANC ≥ 0.75 × 10^9/L and a platelet count ≥ 25 × 10^9/L; restart at 1 dose level ↓. Discontinue if no recovery within 2 weeks.
Grade 3 or 4 non-hematologic toxicity (see table D for neurotoxicity)	Hold until recovery to ≥ grade 2; restart at 1 dose level ↓. Consider discontinuing for grade 4 toxicity.
Pneumonitis	Hold and investigate; discontinue if confirmed.

Any grade PRES/ PML/ or dose-limiting toxicity at 0.7 mg/m2	Discontinue.

Table D:

- 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/m2) 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.

Dosage with 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 0.5mg/m^2 based on patient tolerability.
> 3 x ULN	Any	

Dosage with 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.

Children:

The safety and effectiveness of bortezomib in children have not been established.

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F - Administration Guidelines

- 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 and protect from light.

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G - Special Precautions

Contraindications:

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

Other Warnings/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 concurrent multiple myeloma and AL amyloidosis, or patients with 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.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been conducted.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Fetotoxicity: Yes
- Mutagenicity: Unlikely
- Teratogenicity: Unlikely
- Pregnancy:
  Bortezomib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Documents in animal studies

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H - Interactions

Bortezomib is metabolized primarily by CYP3A4 and 2C19. Bortezomib is a poor inhibitor of CYP 1A2, 2C9, 2D6, 3A4 and 2C19 and does not induce CYP1A2 or CYP3A4 in vitro. In addition, bortezomib does not appear to be a substrate for p-glycoprotein (Pgp) and several other drug efflux pumps. No significant drug-drug interaction was observed with bortezomib and omeprazole (potent CYP2C19 inhibitor).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Hypoglycemic agents (e.g. glyburide, metformin, pioglitazone, rosiglitazone, repaglinide etc.)	Potential hypoglycemia or hyperglycemia	Unknown	Close monitoring of blood glucose and dose adjustment of antidiabetic agent as necessary
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)	↑ bortezomib exposure (up to 35%) and potential ↑ in toxicity	↓ metabolism of bortezomib	Caution for use of strong CYP3A4 inhibitors; monitor for toxicity
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ bortezomib exposure (up to 45%) and potential ↓ in efficacy	↑ metabolism of bortezomib	Avoid strong CYP3A4 inducers; no significant effect observed for dexamethasone (weaker CYP3A4 inducer)
Drugs Associated with Peripheral Neuropathy (e.g. amiodarone, statins)	Potential ↑ in neurotoxicity	Additive effect	Monitor and adjust dose accordingly
Hypotensive Agents	Potential ↑ in hypotension	Additive effects	Monitor and adjust hypotensive agents accordingly
High dose cytarabine and daunorubicin	↑ risk of ARDS	Unknown	Avoid concomitant use

Green tea and preparations containing green tea	In laboratory studies, may reduce bortezomib activity	Unknown	Avoid use during treatment duration
Vitamin C supplements	In laboratory studies, may suppress or eliminate bortezomib activity	Formation of inactive complex with bortezomib; appears to be dose-dependent	Avoid use of vitamin C supplements during treatment. If must give, suggest vitamin C (up to 500mg) given at least 12 h before or after bortezomib

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Chest x-ray	Baseline, then CXR and lung function assessment if ILD is suspected
CBC with differential	Baseline and as clinically indicated (at minimum, prior to each cycle); monitor platelets before each dose
Liver and renal function tests, electrolytes	Baseline, at each cycle and as clinically indicated
Blood glucose levels, especially in patients using antidiabetic medications	Baseline 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

Monitor Type	Monitor Frequency
LVEF monitoring in patients with cardiac risk factors	Baseline and as clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Bortezomib - Previously Untreated - Multiple Myeloma
- Bortezomib - Previously Untreated - Multiple Myeloma Pre-Stem Cell Transplant
- Bortezomib - Relapsed or Refractory Multiple Myeloma
- Bortezomib - In Combination with Lenalidomide and Dexamethasone for Previously Untreated Multiple Myeloma Without Intent for Stem Cell Transplantation
- Daratumumab and Bortezomib in combo with Cyclophosphamide and Dexamethasone - Previously Untreated Light Chain (AL) Amyloidosis
- Bortezomib - Previously Untreated Transplant Ineligible Mantle Cell Lymphoma
- Bortezomib - In Combination with Selinexor and Dexamethasone for Previously Treated Multiple Myeloma
- Bortezomib - In Combination with Lenalidomide and Dexamethasone for Previously Untreated Multiple Myeloma Pre-SCT

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K - References

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November 2024 Updated Pregnancy and Lactation section

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L - Disclaimer

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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