

[Drug Name](#) | [Mechanism of Action & Pharmacokinetics](#) | [Indications & Status](#) | [Adverse Effects](#) | [Dosing](#) | [Administration Guidelines](#) | [Special Precautions](#) | [Interactions](#) | [Recommended Clinical Monitoring](#) | [References](#)

A DRUG NAME: BORTEZOMIB

SYNONYM(S): N-pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid ; [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.; PS-341; MLN-341

COMMON TRADE NAME(S): Velcade® (Janssen-Ortho)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Bortezomib is a modified dipeptidyl boronic acid. It is a reversible inhibitor of 26S proteasome, a large protein complex that degrades ubiquitinated proteins. Inhibition of the proteasome pathway affects multiple signaling cascades within cells, inhibiting NFκB and leading to accumulation of p27. Pharmacodynamic studies show a 60-70% reduction in 20S proteasome activity after treatment with bortezomib. Bortezomib has been studied in phase III trials in previously treated as well as chemotherapy-naïve patients with multiple myeloma and in phase II studies in mantle cell lymphoma.

Oral Absorption	No	
Distribution	After IV administration, more than 90% of the drug is rapidly cleared from the plasma within minutes. Multiple doses lead to an increase in AUC due to a reduction in clearance. The volume of distribution is large (up to 1884 L/m ²)	
	Cross blood brain barrier?	No
	PPB	83%
Metabolism	Bortezomib is metabolized by cytochrome P450 liver microsomes (Major: 3A4 and 2C19; Minor: 2D6, 2C9, and 1A2) into several inactive deboronated hydroxylated metabolites and inhibits 1A2, 2C9, 2D6, 3A4 and 2C19. Clearance may be reduced in patients with hepatic impairment.	
	active metabolite(s)	No
	inactive metabolite(s)	Yes
Excretion	t _{1/2} (elimination)	50-110 hours

[Back to Top](#)

C INDICATIONS AND STATUS

- * Progressive multiple myeloma in patients who have received at least one prior treatment and who have already undergone, or are unsuitable for, stem cell transplantation.
- * As part of combination therapy for the treatment of patients with previously untreated multiple myeloma who are unsuitable for stem cell transplantation
- * Treatment of patients with mantle cell lymphoma who have relapsed or are refractory to at least one prior therapy

* Health Canada approved indication

▲ [Back to Top](#)

D ADVERSE EFFECTS: Adverse effects that occurred in at least 10% of patients, OR were considered severe or life threatening. Frequency is presented as the worst reported for either single agent or combination therapy.

ORGAN SITE	SIDE EFFECT*	ONSET**	
Cardiovascular	Orthostatic hypotension (15%)	I	E
	Arrhythmia, QTc prolongation, pericarditis/effusion (rare)	I	E
	Arterial/venous thromboembolism (rare)		E D
	Edema (28%), Hypertension (13%)		E
	Myocardial ischemia/infarction (rare)		E
	Decreased left ventricular ejection fraction, heart failure (5%)	I	E
Dermatologic and Hypersensitivity	Rash (28%)	I	E
	Injection site reaction (rare)	I	
	Hypersensitivity, angioedema (rare)	I	
Extravasation hazard (refer to Appendix 2)	Irritant	I	
Gastrointestinal	Nausea (64%) Vomiting (35%)	I	
	Heartburn (13%)	I	
	Dehydration (18%), mucositis		E
	GI hemorrhage, obstruction, perforation (rare)		E
	Diarrhea (58%)	I	E
	Anorexia (43%), loss of weight (11%)	I	
	Constipation (50%), ileus (rare)		E
	Abdominal Pain (20%), pancreatitis (rare)	I	

D	ADVERSE EFFECTS (continued): Adverse effects that occurred in at least 10% of patients, OR were considered severe or life threatening. Frequency is presented as the worst reported for either single agent or combination therapy.		
	ORGAN SITE	SIDE EFFECT*	ONSET**
	Musculoskeletal	Arthralgia (28%)	E
		Back, bone pain (17%)	E
		Myalgia, muscle cramps (26%)	E
	Pulmonary	Dyspnea (29%), pleural effusion (rare)	E
		Pneumonitis/ Acute Respiratory Distress Syndrome (ARDS) – rare	E
		Cough (21%)	E
	Generalized	Fatigue, malaise, weakness (72%)	E
		Infection (pneumonia, herpes zoster) (18%)	E
		Pain (10%), pyrexia (36%), rigors (12%)	E
		Tumour Lysis syndrome	E
		Hypo/hyperglycemia (diabetics)	E
	Hematologic	Thrombocytopenia (37% - Grade 3 or 4)	E
		Bleeding, epistaxis (10%); Disseminated Intravascular Coagulation (DIC) –rare	E
		Anemia, lymphopenia (19% grade 3 or 4)	E
		Neutropenia (40% grade 3 or 4)	E
	Neurological	<u>Peripheral/autonomic neuropathy (55%)</u>	E
		Blurred vision (11%)	E
		Seizures, RPLS (rare)	E
		Hearing loss, ataxia (rare)	E
		Anxiety (14%), dysgeusia (13%)	E
		Confusion, encephalopathy (rare)	E

D	ADVERSE EFFECTS (continued): Adverse effects that occurred in at least 10% of patients, OR were considered severe or life threatening. Frequency is presented as the worst reported for either single agent or combination therapy.		
	ORGAN SITE	SIDE EFFECT*	ONSET**
Neurological (cont.)		TIA /Stroke/hemorrhage (rare)	E
		Insomnia (27%)	E
		Headache (28%)	E
		Dizziness (23%)	I E
Renal		Renal failure, nephrotic syndrome (rare)	E
		Hematuria (rare)	E
		Electrolyte abnormality, SIADH (rare)	E
Hepatic		Acute Hepatic Failure (Rare)	D
		Portal vein thrombosis /cholestasis(rare)	E
		Abnormal LFTs, including bilirubin	E

* Dose-limiting side effects are underlined.

** 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 adverse events reported are gastrointestinal side effects, cytopenias (especially thrombocytopenia), fatigue, and peripheral neuropathy. Myelosuppression was more common in the myeloma studies, while neuropathy and rash were more common in the mantle cell lymphoma studies. In the phase III study of melphalan/prednisone ± bortezomib, myelosuppression, lymphopenia, nausea, diarrhea, vomiting, constipation, neuropathy, infection (including herpes zoster), hypertension and hypotension were all more common in the bortezomib arm.

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

Thrombocytopenia is common and early with recovery by day 21, but does not appear to be cumulative. Thrombocytopenia is more severe in patients with low platelets prior to therapy. CNS and GI bleeds have been reported. Complete blood counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is $< 25 \times 10^9/L$ and reinitiated at a reduced dose. Transfusions may be used at the discretion of the physician.

Bortezomib causes a dose-related and cumulative **peripheral neuropathy** that is predominantly sensory, although cases of mixed sensory-motor neuropathy have also been reported. 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. The neuropathy appears reversible in 14% of patients. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of bortezomib. Autonomic neuropathy may occur. Bortezomib treatment can cause orthostatic/postural **hypotension**. These events can occur throughout therapy and may be more common in patients with pre-existing hypertension. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids or sympathomimetics.

D ADVERSE EFFECTS (continued)

Hypertension has also been reported, and rarely, patients may present with reversible posterior leukoencephalopathy syndrome (RPLS) 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. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib. There is limited rechallenge information in these patients.

Bortezomib is a cytotoxic agent and can rapidly kill malignant cells resulting in **tumor lysis syndrome**, especially in patients with high tumor burden. Such patients should be monitored closely and appropriate precautions taken.

▲ [Back to Top](#)

E DOSING

Refer to protocol by which patient is being treated. Bortezomib has a narrow therapeutic index and should be used with caution. Doses should be administered at least 72 hours apart 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.

Dose levels of bortezomib are 1.3, 1 and 0.7 mg/m²

Adults:

- Single Agent: Bortezomib 1.3 mg/m² IV on Days 1, 4, 8, 11; q 3 weekly for up to 8 cycles
- For patients with continuing response after 8 cycles consider continuation with a q 5w schedule (Day 1, 8, 15, 22, q 5 weekly)
- In Combination: Prior to cycle, ensure platelets $\geq 70 \times 10^9/L$ and ANC $\geq 1 \times 10^9/L$ and other toxicity \leq grade 1 (or recovered to baseline)
- Melphalan 9mg/m² + prednisone 60mg/m² P.O. days 1-4, q 6 weekly.
- Bortezomib: Cycle 1-4 - 1.3 mg/m² IV on Days 1, 4, 8, 11, 22, 25, 29, 32, q 6 weekly
Cycle 5-9 - 1.3 mg/m² IV on Days 1, 8, 22, 29, q 6 weekly

Dosage Modifications for Hematological and Non-Hematological Toxicities:

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

A: Single Agent	Dose modification and delay
AGC $\leq 0.5 \times 10^9/L$ or platelets $< 25 \times 10^9/L$	Delay until recovery and reduce 1 dose level
Grade 2 drug-related fluid retention *	Reduce 1 dose level
Grade 3 or 4 drug-related fluid retention *	Discontinue
\geq grade 3 non-hematologic toxicity (see Table C for neurotoxicity)	Hold until \leq grade 1/baseline then restart with 1 dose level ↓
If no recovery after delay	Discontinue

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

E DOSING (continued)

Dosage Modifications for Hematological and Non-Hematological Toxicities (continued):

B: In Combination	Dose modification and delay
Toxicity Prior Cycle / Day 1 of Cycle	
Day 1 AGC < $1 \times 10^9/L$ or platelets < $70 \times 10^9/L$	Delay until recovery
Grade 4 AGC or platelets ≥ 5 days or febrile neutropenia or thrombocytopenic bleeding PRIOR cycle	Reduce Melphalan dose by 25%
Bortezomib held (≥ 3 times C1-4 or ≥ 2 times C5-9)	Reduce Bortezomib by 1 dose level
\geq grade 3 non-hematologic toxicity (see table C for neurotoxicity)	Hold until \leq grade 1/baseline then restart with 1 dose level ↓
Toxicity During Cycle	
ANC $\leq 0.75 \times 10^9/L$ or platelet $\leq 30 \times 10^9/L$	Hold both bortezomib and melphalan (if applicable)
\geq grade 3 non hematologic toxicity (see table C for neurotoxicity)	Hold until \leq grade 1/baseline then restart with 1 dose level ↓

Dosage for Neurotoxicity:

Patients with pre-existing severe neuropathy should be treated with Bortezomib only after careful risk/benefit assessment.

C: Severity of Peripheral Neuropathy	Dosage and Regimen Modification
Grade 1 (paresthesias 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)	Reduce dose to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves. When toxicity resolves reinitiate at a reduced dose of 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 OR RPLS (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue permanently

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:¹

Bilirubin	AST	Starting Dose
$\leq 1 \times \text{ULN}$	$> \text{ULN}$	No change
$> 1 - 1.5 \times \text{ULN}$	Any	No change
$> 1.5 - 3 \times \text{ULN}$	Any	First cycle: ↓ to 0.7 mg/m^2 .
$> 3 \times \text{ULN}$	Any	Subsequent cycles: Consider ↑ dose to 1.0 mg/m^2 or further ↓ dose to 0.5 mg/m^2 based on patient tolerability.

¹Information obtained from bortezomib US prescribing information, December 2009

E DOSING (continued)*Dosage with Renal Impairment:*²

Dose adjustments are not necessary in patients with renal insufficiency. 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.

(²Information obtained from bortezomib US prescribing information, December 2009)

Dosage in the elderly:

There is no evidence to suggest that dosage adjustments are necessary in elderly patients

Children:

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

▲ [Back to Top](#)

F ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

Administered as a 3- to 5-second IV push followed by a standard saline flush; no central line is required.

▲ [Back to Top](#)

G SPECIAL PRECAUTIONS

Bortezomib is **contraindicated** in patients with hypersensitivity to bortezomib, boron, mannitol, or other excipients. Caution should be exercised when driving or using machinery, and in patients on medication(s) that may lead to hypotension due to the risk of hypotension, dizziness and syncope, as well as in patients with amyloidosis.

Bortezomib is **clastogenic** and **fetotoxic** but not mutagenic in animals. Women of childbearing potential should avoid becoming **pregnant** while being treated with bortezomib. If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. **Fertility** is affected in animal studies. Effective contraception should be used by both genders during treatment and for at least 3 months after treatment completion.

Carcinogenicity studies have not been conducted with bortezomib. It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bortezomib, women should be advised against **breast feeding** while being treated with bortezomib.

▲ [Back to Top](#)

H	INTERACTIONS			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Hypoglycemic agents (e.g. glyburide, metformin, pioglitazone, rosiglitazone, repaglinide etc.)	Potential Hypoglycemia or Hyperglycemia	Unknown	Close monitoring of blood glucose
	Inhibitors of cytochrome P450 3A4 / 2C19(e.g. erythromycin, ketoconazole, cimetidine, aprepitant)	Potential increase of toxicity	Potentially reduced clearance of bortezomib	Monitor for toxicity
	Inducers of cytochrome P450 3A4/2C19(e.g. barbiturates, glucocorticoids, phenytoin, St John's Wort etc.)	Potential decrease of efficacy	Potentially increased clearance of bortezomib	Monitor for reduced efficacy
	Drugs metabolized by 1A2, 2C9, 2D6, 3A4, 2C19.	Increased toxicity of these drugs	Bortezomib is a weak inhibitor	Use with caution
	Drugs Associated with Peripheral Neuropathy (e.g. amiodarone, statins)	Potential increase of neurotoxicity	Additive effect	Monitor and adjust dose accordingly
	Hypotensive Agents	Potential increase of hypotension	Additive effects	Monitor and adjust hypotensive agents accordingly
	High dose cytarabine and daunorubicin	Increased 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

▲ [Back to Top](#)

I

RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring**

- Baseline CXR
- Monitor blood counts at each visit
- Baseline and regular hepatic function tests
- Baseline and regular renal function tests
- Routine toxicity ratings of fatigue, gastrointestinal side effects at each visit
- Regular blood pressure monitoring at each visit
- Close monitoring for symptoms of neuropathy, including constipation
- Grade toxicity using the current [NCI Common Toxicity Criteria Version](#)

Suggested Clinical Monitoring

- Baseline and regular uric acid monitoring
- LVEF monitoring in patients with cardiac risk factors

▲ [Back to Top](#)

J

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▲ [Back to Top](#)