DRUG NAME: Bortezomib

SYNONYM(S): PS-341; MLN-341

COMMON TRADE NAME(S): VELCADE®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Bortezomib is a reversible inhibitor of the 26S proteasome, a protein complex that degrades ubiquitinated proteins. This inhibition affects cancer cells in a number of ways, including altering regulatory proteins, which control cell cycle progression and Nuclear Factor kappa B activation. Inhibition of the proteasome results in cell cycle arrest and apotosis,[1] generally during the G_2-M phase of the cell cycle.[2]

PHARMACOKINETICS:

Interpatient variability	wide interpatient variability in plasma concentration	
Distribution	distribution half life is less than 10 minutes[3]	
	cross blood brain barrier?	no information found
	volume of distribution[4]	>500 L
	plasma protein binding	no information found
Metabolism	oxidative deboronation via CYP 3A4 and 2C19; other CYP 450 enzymes (1A2, 2C9, 2D6) have minor roles; Mean AUC values are increased by 60% in moderate to severe liver impairment.[5]	
	active metabolite(s)	none
	inactive metabolite(s)[3]	>30
Excretion	urine	no information found
	feces	no information found
	terminal half life	9-15 h
	clearance	no information found

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Multiple myeloma
*Lymphoma, non-Hodgkin

Other uses:
Amyloidosis[6,7]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to boron[1]

Caution:
- all lymphoma and myeloma patients should be screened for ***Hepatitis B (HBV) reactivation***[8]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***[9]
- ***herpes zoster reactivation*** may occur; antiviral prophylaxis is suggested for all patients.[10-12]
- risk of ***peripheral neuropathy*** may be increased when bortezomib is used concomitantly with other drugs associated with peripheral neuropathy (e.g., amiodarone, antiviral agents, isoniazid, nitrofurantoin, and HMG-CoA reductase inhibitors)[13]
- ***overdosage*** with as little as twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes[1]; in the event of an overdosage, monitor vital signs and provide supportive care to maintain blood pressure and body temperature[1]

Special Populations:
- greater sensitivity of ***elderly*** patients cannot be ruled out; however, no overall differences in safety or effectiveness were observed between younger patients and patients >65 years of age[1]
- patients on oral ***antidiabetic*** agents receiving bortezomib may experience either hypo- or hyperglycemia; monitor blood glucose levels closely[1]; dose adjustment of oral hypoglycemics may be required[14]
- patients with ***amyloidosis*** should be treated with caution as the impact of proteasome inhibition on disorders associated with protein accumulation is unknown[1]
- risk of ***hypotension*** may be increased when bortezomib is used with medications that can cause hypotension[13]; dose adjustment of hypotensive agents may be required[13]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and in the mammalian *in vivo* mutation test. Bortezomib is clastogenic in mammalian *in vitro* chromosome tests.[1]

Fertility: Fertility studies have not been performed. Degenerative effects in ovaries and testes suggest a potential effect on fertility.[1]

Pregnancy: In animal studies, bortezomib caused post-implantation losses, but was not teratogenic at the highest tested doses. Contraception is recommended for males and females of child-bearing potential during treatment with bortezomib and for 3 months following treatment.[15]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[16] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.[17-20]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	hypersensitivity reactions (<1%)
	cutaneous vasculitis[21-23]
blood/bone marrow/ febrile neutropenia	anemia (26-32%, severe 9-10%)
	neutropenia (19-24%, severe 14-16%)
	thrombocytopenia[1] (35-43%, severe 30%); nadir day 11; see paragraph following **Side Effects** table
auditory/hearing	hearing loss (<1%)[24]
cardiovascular (arrhythmia)	arrhythmias (<1%)
cardiovascular (general)	congestive heart failure; decreased left ventricular ejection fraction (<1%)
	hypotension (11-12%, severe 4%); see paragraph following **Side Effects** table
	ischemia, infarction, angina (<1%)
	pulmonary hypertension (<1%)
coagulation	disseminated intravascular coagulation (<1%)
constitutional symptoms	fatigue[25] (61-65%, severe 12-18%)
	fever (35-36%, severe 4-6%)
	insomnia (18%)
	rigors (11-12%)
dermatology/skin	*extravasation hazard:* irritant[1]
	pruritis (12%)
	rash, urticaria[26] (24-28%, severe 2%)
endocrine	ADH secretion abnormalities (<1%)
gastrointestinal	*emetogenic potential:* rare[16,27]
	anorexia (34-43%, severe 2-3%)
	constipation[1] (42-43%, severe 2%)
	dehydration[1] (18%, severe 7%)
	diarrhea[1] (55-58%, severe 7-8%); see paragraph following **Side Effects** table
	dyspepsia (10-13%)
	enteritis (<1%)[28]
	ileus, obstruction (<1%)
	nausea[1] (57-64%, severe 2-7%)
	stomatitis (<1%)
	taste alterations, dysgeusia (13%)
	vomiting[1] (35-36%, severe 3-7%)
hemorrhage	***epistaxis*** (10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	severe hemorrhage (<1%)
hepatobiliary/pancreas	liver failure (<1%)[29]; see paragraph following **Side Effects** table
	acute pancreatitis (<1%)
infection	***febrile neutropenia*** (<1%)[25]
	herpes zoster (11-13%, severe 1%)
	nasopharyngitis (14%)
	pneumonia (10%, severe 5%)
	sepsis (<1%)
	upper respiratory tract infection (18%)
lymphatics	peripheral edema (17-21%, severe 1%)
metabolic/laboratory	asymptomatic increases in liver enzymes (<1%)
	electrolyte abnormalities (<1%)
	hyperbilirubinemia (<1%)
	hyperuricemia; during periods of active cell lysis (<1%); see paragraph following **Side Effects** table
musculoskeletal	arthralgia (15-28%, severe 5%)
	muscle cramps (24%)
neurology	dizziness excluding vertigo (14-21%, severe 1%)
	encephalopathy (<1%)
	headache (28%, severe 4%)
	insomnia (18-27%, severe 1%)
	hypoesthesia (11%)
	mood alterations, anxiety (14%)
	peripheral neuropathy[25] (36-37%, severe 8-14%); see paragraph following **Side Effects** table
	psychosis (<1%)
	seizures (<1%)
	sensory neuropathy, paresthesias (14-21%, severe 2%)
ocular/visual	blurred vision (11%, severe 1%)
	diplopia (<1%)
pain	abdominal pain (16-20%, severe 2%)
	back pain (14%, severe 3-4%)
	bone pain (16-17%, severe 4-5%)
	limb pain (15%, severe 2%)
	musculoskeletal pain (10%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	not otherwise specified (10%, severe 1-2%)
pulmonary	cough (17-21%)
	dyspnea (25-29%, severe 5%)
	pulmonary toxicity, respiratory failure (<1%)[30]
renal/genitourinary	renal failure (<1%)
sexual/reproductive function	infertility, sterility
syndromes	Sweet syndrome (<1%)[31,32]
	tumor lysis syndrome (<1%)[33,34]

Adapted from standard reference[1] unless specified otherwise.

Diarrhea is a common side effect in patients receiving bortezomib; severe diarrhea occurs in 7-8% of patients. Management of diarrhea should include, maintaining adequate fluid intake and prompt treatment with loperamide. Patients with severe diarrhea should be carefully monitored for dehydration and given fluid and electrolyte replacement as needed.[1] Premedication with loperamide prior to bortezomib treatment is not required. However, patients should be instructed to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent bowel movement than usual. If NCI Grade 3 diarrhea occurs,[1] or if diarrhea is associate with mucus or dehydration,[35] discontinue treatment until diarrhea resolves, then reinitiate at a 25% dose reduction.

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[36] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[37]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[38] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[39]

Hypotension occurs in up to 12% of patients receiving bortezomib. Risk factors include history of syncope, concomitant use of medications known to lower blood pressure, and dehydration.[3] Hydration status should be assessed and corrected before and if necessary throughout bortezomib therapy, especially in patients experiencing vomiting and diarrhea.[3] Additionally, dosage adjustment of hypotensive agents may be necessary.[13] Mineralocorticoids and/or sympathomimetics may be effective in minimizing the hypotensive effects of bortezomib.[1] Patients should be instructed to report signs and symptoms of hypotension (lightheadedness, dizziness, syncope) immediately.[1] In patients experiencing NCI Grade 3 hypotension, discontinue bortezomib until symptoms resolve, and then reinitiate at a 25% dose reduction.[1]

Rare cases of acute ***liver failure*** have been reported in bortezomib-treated patients on multiple concomitant medications and with serious underlying medical conditions.[1] Other reported hepatic events include asymptomatic

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increases in liver enzymes, hyperbilirubinemia, and hepatitis.[1] These changes may be reversible upon discontinuation of bortezomib.[1]

Peripheral Neuropathy is a common, and often dose limiting side effect. It is predominantly sensory, characterized by pain, paresthesias, burning dysethesias, and numbness, with feet affected more often than hands.[40] Cases of mixed sensorimotor neuropathy have also been reported.[1] The mechanism underlying bortezomib-induced peripheral neuropathy is not known.[1] Patients with baseline symptoms are at a greater risk of developing severe neuropathy.[3] Early detection and appropriate dosage adjustments may prevent development of severe neuropathies.[3,40] The development of even mildly painful peripheral neuropathy should prompt a dose reduction. Autonomic neuropathy may contribute to postural hypotension, diarrhea, constipation with ileus, and pyrexia caused by bortezomib.[1]

Patients receiving bortezomib experience a median 60% ***decrease in platelet count*** regardless of initial baseline platelet count, baseline serum myeloma protein level, or degree of bone marrow involvement.[3] This pattern of thrombocytopenia is not consistent with the pattern typically observed with conventional chemotherapy.[19] The onset of thrombocytopenia most commonly occurs after cycle 1 or 2 and continues throughout therapy, with no evidence of cumulative thrombocytopenia.[3,40] Platelet counts typically reach a nadir on day 11 and rise to a normal count by day 21.[3] In responding patients, platelet counts at baseline appear to increase progressively with successive cycles of treatment from the second cycle onwards.[40] The mechanism underlying bortezomib-induced thrombocytopenia is not known, but it is unlikely to be related to marrow injury or decreased thrombopoietin production[41]; therefore, supportive care rather than discontinuation of bortezomib therapy may be appropriate.[3] Bortezomib should be temporarily discontinued in patients with a platelet count less than 25, (NCI Grade 4 thrombocytopenia) until the platelet count returns to normal. Bortezomib can then be reinitiated at a 25% dose reduction.[3] There have been reports of GI and intracerebral hemorrhage in association with bortezomib-induced thrombocytopenia.[13]

Subcutaneous administration of bortezomib appears to be comparable with intravenously administered bortezomib in terms of overall systemic availability and response rates in multiple myeloma, but may have an improved safety profile, with fewer dose reductions and discontinuations due to adverse events. In particular, peripheral neuropathy events, including grade 2 and 3 events, are reported less frequently with subcutaneous dosing. Reversible redness at the administration site is the main local reaction, although severe injection reactions were reported in 1% of patients.[42,43]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ascorbic acid[2,44-46]	suppresses or eliminates the ability of bortezomib to induce apoptosis and growth arrest in cancer cells; may be dose dependent	probably direct chemical interaction (through the binding of ascorbic acid to bortezomib, creating a biologically inactive complex)	avoid vitamin C supplements if possible; otherwise take vitamin C at least 12 h before or after bortezomib (at a suggested maximum dose of 500 mg)[45]
dexamethasone[14,47]	bortezomib Cmax reduced by 20%; no change in mean AUC	weak CYP 3A4 induction by dexamethasone	not expected to affect clinical efficacy
docetaxel[3]	no effect on bortezomib or docetaxel pharmacokinetics or pharmacodynamics		
gemcitabine[3]	no effect on bortezomib or gemcitabine pharmacokinetics or pharmacodynamics		

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AGENT	EFFECT	MECHANISM	MANAGEMENT
ascorbic acid[2,44-46]	suppresses or eliminates the ability of bortezomib to induce apoptosis and growth arrest in cancer cells; may be dose dependent	probably direct chemical interaction (through the binding of ascorbic acid to bortezomib, creating a biologically inactive complex)	avoid vitamin C supplements if possible; otherwise take vitamin C at least 12 h before or after bortezomib (at a suggested maximum dose of 500 mg)[45]
green tea and preparations made from green tea[48]	bortezomib efficacy severely decreased, if not obliterated	unspecified antagonism	avoid green tea and preparations made from green tea throughout entire course of treatment
irinotecan[3]	no effect on bortezomib or irinotecan pharmacokinetics or pharmacodynamics		
ketoconazole[14]	effects variable; mean bortezomib AUC increased by 35%	strong CYP 3A inhibition by ketoconazole	use combination with caution; monitor for bortezomib side effects
rifampicin[14,47]	mean bortezomib AUC reduced by 45%; bortezomib Cmax reduced by 23%; possible reduction in clinical antitumour effect	strong CYP 3A4 induction by rifampicin	avoid combination if possible

Bortezomib is a **substrate** for CYP 3A4, CYP 2C19, CYP 1A2, CYP 2D6, and CYP 2C9. Concomitant use of strong **CYP 3A4 inducers** is not recommended due to the potential for reduced efficacy of bortezomib. Monitor for bortezomib side effects during concomitant therapy with strong **CYP 3A4 inhibitors**.[14] Significance of interactions due to other enzyme pathways is not clear.

Bortezomib is a **weak inhibitor** of CYP 1A2, CYP 2C9, CYP 2D6, CYP 3A4, and CYP 2C19.[14] Clinical significance is not known.

SUPPLY AND STORAGE:

Injection:
Apotex Inc., Janssen Inc., Marcan Pharmaceuticals Inc., Pharmascience Inc., and Teva Canada Ltd. (Actavis) supply bortezomib as 3.5 mg vials of preservative free lyophilized powder for injection. Store at room temperature. Protect from light.[14,49-52]

Juno Pharmaceuticals Corp (previously MDA Inc.) and Taro Pharmaceuticals Inc. supply bortezomib as 1 mg, 2.5 mg, and 3.5 mg vials of preservative free lyophilized powder for injection. Store at room temperature. Protect from light.[53,54]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility of selected drugs: consult detailed reference

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Additional information: Bortezomib is prepared as a different concentration for each route of administration. When intended for subcutaneous administration, bortezomib is reconstituted to provide a more concentrated final solution (final concentration = 2.5 mg/mL), than when it is intended for intravenous administration (final concentration = 1 mg/mL).[12]

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous[43,55-58]	***rotate sites on thighs and abdomen***
Intramuscular	no information found
Direct intravenous[56-59]	over 3-5 seconds
Intermittent infusion	no information found
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	**ABSOLUTELY CONTRAINDICATED: INTRATHECAL INJECTION CAN BE FATAL**
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Subcutaneous:	***3 weeks***[56,57]:	***1.3 mg/m²*** (range 1-1.3 mg/m²) ***SC for one dose on days 1, 4, 8, and 11.*** (total dose per cycle 5.2 mg/m² [range 4-6 mg/m²]) Consecutive doses should be separated by at least 72 hours.[1]
	4 weeks[57]:	***1.3 mg/m²*** (range 1-1.5 mg/m²) ***SC for one dose on days 1, 8, 15, and 22.*** (total dose per cycle 5.2 mg/m² [range 4-6 mg/m²])
	5 weeks[56,58]:	***1.3 mg/m²*** (range 1-1.5 mg/m²) ***SC for one dose on days 1, 8, 15, and 22.*** (total dose per cycle 5.2 mg/m² [range 4-6 mg/m²])

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BC Cancer usual dose noted in ***bold, italics***

Intravenous:

3 weeks[56,57,59]: 1.3 mg/m^2 (range 1-1.3 mg/m^2) IV for one dose on days 1, 4, 8, and 11.
(total dose per cycle 5.2 mg/m^2 [range 4-5.2 mg/m^2])
Consecutive doses should be separated by at least 72 hours.

For maintenance therapy (beyond 8 cycles) standard doses may be used, or 1.3 mg/m^2 (range 1-1.3 mg/m^2) IV for one dose on days 1, 8, 15, and 22 of a 5 week cycle.[1]
(total dose per cycle 5.2 mg/m^2 [range 4-5.2 mg/m^2])

4 weeks[57]: 1.3 mg/m^2 (range 1-1.5 mg/m^2) IV for one dose on days 1, 8, 15, and 22.
(total dose per cycle 5.2 mg/m^2 [range 4-6 mg/m^2])

5 weeks[56,58]: 1.3 mg/m^2 (range 1-1.5 mg/m^2) IV for one dose on days 1, 8, 15, and 22.
(total dose per cycle 5.2 mg/m^2 [range 4-6 mg/m^2])

6 weeks[59]: Cycles 1-4: 1.3 mg/m^2 IV for one dose on days 1, 4, 8, 11, 22, 25, 29, and 32.
(total dose per cycle 10.4 mg/m^2)
Consecutive doses should be separated by at least 72 hours.

Cycles 5-9: 1.3 mg/m^2 IV for one dose on days 1, 8, 22, and 29.
(total dose per cycle 5.2 mg/m^2)

Dosage in myelosuppression[1]*:* at the onset of any NCI Grade 4 hematological toxicities, discontinue bortezomib until symptoms resolve; reinitiate at a 25% dose reduction

Dosage in renal failure[60-62]*:* starting dose adjustments are not necessary, regardless of degree of renal failure

Dosage in hepatic failure[5]

Suggested dose modification

	Serum bilirubin	AST	Dose
mild	≤ 1xULN	> ULN	100%
	1-1.5xULN	any	100%
moderate	>1.5-3xULN	any	reduce to 0.7 mg/m^2 for first cycle*
severe	>3xULN	any	

* For subsequent cycles: may consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 based on patient tolerability.

Dosage in dialysis[60-63]: has been given safely to patients on hemodialysis without dose reduction; administer bortezomib dose after dialysis procedure

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Dosage in neuropathy[1]*:*

Peripheral neuropathy	
NCI Grade (value)	**bortezomib dose**
Grade 1 without pain or loss of function	maintain dose
Grade 1 with pain or Grade 2	reduce dose[29] by 25%,
Grade 2 with pain or Grade 3	hold bortezomib until symptoms resolve; reinitiate at 0.7 mg/m^2 once weekly
Grade 4	discontinue bortezomib

Dosage in diarrhea[35]*:*

delay next cycle until diarrhea resolves(< 2 watery bowel movements/day)

NCI Grade (value) for severity of diarrhea with last cycle	bortezomib dose this cycle
≤ grade 2 (4-6 stools/day more)	no change from previous cycle
≥ grade 3 (7-9 stools/day more) or associated with mucus or dehydration	reduce dose[8,35] by 20-25% of that used in the last course (if two dose reductions have already occurred, further treatment must be individualized and should only continue if a clearly useful clinical response has occurred)

Dosage in other non-hematological toxicities[1]*:*

at the onset of any NCI Grade 3 non-hematological toxicities, discontinue bortezomib until symptoms resolve; reinitiate at a 25% dose reduction

Children:

has been used[64,65]

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