

1 **VELCADE™ (bortezomib) for Injection**

2 **PRESCRIBING INFORMATION**

3 **DESCRIPTION**

4

5 VELCADE™ (bortezomib) for Injection is an antineoplastic agent available for
6 intravenous injection (IV) use only. Each single dose vial contains 3.5 mg of bortezomib
7 as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

8

9 Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol
10 boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium
11 with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its
12 cyclic anhydride form as a trimeric boroxine.

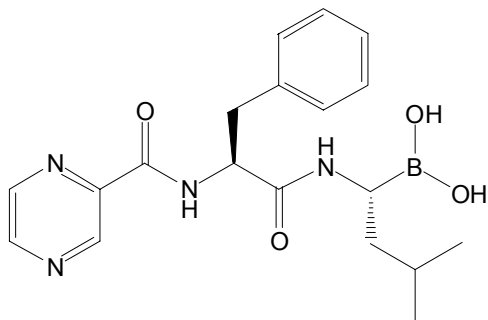
13

14 The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-
15 [[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

16

17 Bortezomib has the following chemical structure:

18



19

20

21 The molecular weight is 384.24. The molecular formula is C₁₉H₂₅BN₄O₄. The solubility
22 of bortezomib, as the monomeric boronic acid, in water is: 3.3-3.8 mg/mL in a pH range
23 of 2-6.5.

24 **CLINICAL PHARMACOLOGY**

25 ***Mechanism of Action***

26 Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S
27 proteasome in mammalian cells. The 26S proteasome is a large protein complex that
28 degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential
29 role in regulating the intracellular concentration of specific proteins, thereby maintaining
30 homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted
31 proteolysis which can affect multiple signaling cascades within the cell. This disruption
32 of normal homeostatic mechanisms can lead to cell death. Experiments have

33 demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*.
34 Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models,
35 including multiple myeloma.

36

37 ***Pharmacokinetics***

38 Following intravenous administration of 1.3 mg/m² dose, the median estimated maximum
39 plasma concentration of bortezomib was 509 ng/mL (range=109-1300 ng/mL) in eight
40 patients with multiple myeloma and creatinine clearance values ranging from 31-169
41 mL/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to
42 15 hours at doses ranging from 1.45 to 2.00 mg/m² in patients with advanced
43 malignancies. The pharmacokinetics of bortezomib as a single agent have not been fully
44 characterized at the recommended dose in multiple myeloma patients.

45

46 ***Distribution***

47

48 The distribution volume of bortezomib as a single agent was not assessed at the
49 recommended dose in patients with multiple myeloma. The binding of bortezomib to
50 human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.

51

52 ***Metabolism***

53

54 *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome
55 P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via
56 cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic
57 pathway is deboronation to form two deboronated metabolites that subsequently undergo
58 hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive
59 as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min
60 after dosing indicate that the plasma levels of metabolites are low compared to the parent
61 drug.

62 ***Elimination***

63

64 The pathways of elimination of bortezomib have not been characterized in humans.

65

66 ***Special Populations***

67

68 ***Age, Gender, and Race:*** The effects of age, gender, and race on the pharmacokinetics of
69 bortezomib have not been evaluated.

70

71 ***Hepatic Impairment:*** No pharmacokinetic studies were conducted with bortezomib in
72 patients with hepatic impairment (see **PRECAUTIONS**).

73

74 ***Renal Impairment:*** No pharmacokinetic studies were conducted with bortezomib in
75 patients with renal impairment. Clinical studies included patients with creatinine
76 clearances values ranging from 13.8 to 220 mL/min (see **PRECAUTIONS**).

77

78 **Pediatric:** There are no pharmacokinetic data in pediatric patients.

79

80 ***Drug Interactions***

81 No formal drug interaction studies have been conducted with bortezomib.

82 *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate of
83 cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 (**see PRECAUTIONS**).

84

85 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9,
86 2D6, and 3A4, with IC₅₀ values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19
87 activity (IC₅₀ = 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for
88 this enzyme.

89

90 Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary
91 cultured human hepatocytes.

92

93 **CLINICAL STUDIES**

94 ***Clinical Study in Relapsed and Refractory Multiple Myeloma***

95

96 The safety and efficacy of VELCADE were evaluated in an open-label, single-arm,
97 multicenter study of 202 patients who had received at least 2 prior therapies and
98 demonstrated disease progression on their most recent therapy. The median number of
99 prior therapies was six. Baseline patient and disease characteristics are summarized in
100 **Table 1**.

101

102 An IV bolus injection of VELCADE 1.3 mg/m²/dose was administered twice weekly for
103 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8
104 treatment cycles. The study employed dose modifications for toxicity (**see DOSAGE
105 AND ADMINISTRATION**). Patients who experienced a response to VELCADE
106 treatment were allowed to continue VELCADE treatment in an extension study.

107

108
109

Table 1: Summary of Patient Population and Disease Characteristics *

	N = 202
Patient Characteristics	
Median age in years (range)	59 (34, 84)
Gender: male/female	60% / 40%
Race: caucasian/black/other	81% / 10% / 8%
Karnofsky Performance Status score ≤ 70	20%
Hemoglobin <100 g/L	44%
Platelet count <75 x 10 ⁹ /L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median $\beta 2$ -microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received All 4 of the Above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

110 * Based on number of patients with baseline data available

111

112 Responses to VELCADE alone are shown in **Table 2**. Response rates to VELCADE
113 alone were determined by an independent review committee (IRC) based on criteria
114 published by Blade and others.¹ Complete response required <5% plasma cells in the
115 marrow, 100% reduction in M protein, and a negative immunofixation test (IF⁻).
116 Response rates using the SWOG criteria are also shown. SWOG response required a
117 $\geq 75\%$ reduction in serum myeloma protein and/or $\geq 90\%$ urine protein.² A total of 188
118 patients were evaluated for response; 9 patients with nonmeasurable disease could not be
119 evaluated for response by the IRC. Five patients were excluded from the efficacy
120 analyses because they had minimal prior therapy.

121

122 Ninety-eight percent of study patients received a starting dose of 1.3 mg/m². Twenty-
123 eight percent of these patients received a dose of 1.3 mg/m² throughout the study, while

124 33% of patients who started at a dose of 1.3 mg/m² had to have their dose reduced during
 125 the study. Sixty-three percent of patients had at least one dose held during the study. In
 126 general, patients who had a confirmed CR received 2 additional cycles of VELCADE
 127 treatment beyond confirmation. The mean number of cycles administered was six.

128

129 The median time to response was 38 days (range 30 to 127 days).

130 The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

131 **Table 2: Summary of Disease Outcomes**

Response Analyses (VELCADE monotherapy)	N = 188	N (%)	(95% CI)
Overall Response Rate (Blade) (CR + PR)		52 (27.7%)	(21, 35)
Complete Response (CR) ¹		5 (2.7%)	(1, 6)
Partial Response (PR) ²		47 (25%)	(19, 32)
Clinical Remission (SWOG) ³		33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)		365 Days	(224, NE)

132 ¹ **Complete Response** required 100% disappearance of the original monoclonal protein from blood and
 133 urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the
 134 bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and
 135 calcium.

136 ² **Partial Response** requires ≥50% reduction in serum myeloma protein and ≥ 90% reduction of urine
 137 myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and
 138 calcium.

139 ³ **Clinical Remission (SWOG)** required ≥75% reduction in serum myeloma protein and/or ≥90%
 140 reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable
 141 bone disease and calcium.

142

143 In this study, the response rate to VELCADE was independent of the number and types
 144 of prior therapies. There was a decreased likelihood of response in patients with either
 145 >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen
 146 in patients with chromosome 13 abnormalities.

147

148 A small dose-response study was performed in 54 patients with multiple myeloma who
 149 received a 1.0 mg/m²/dose or a 1.3 mg/m²/dose twice weekly for two out of three weeks.
 150 A single complete response was seen at each dose, and there were overall (CR + PR)
 151 response rates of 30% (8/27) at 1.0 mg/m² and 38% (10/26) at 1.3 mg/m².

152 **INDICATIONS AND USAGE**

153 VELCADE™ (bortezomib) for Injection is indicated for the treatment of multiple
154 myeloma patients who have received at least two prior therapies and have demonstrated
155 disease progression on the last therapy.

156 The effectiveness of VELCADE is based on response rates (**see CLINICAL STUDIES**
157 **section**). There are no controlled trials demonstrating a clinical benefit, such as an
158 improvement in survival.

159 **CONTRAINDICATIONS**

160 VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron or
161 mannitol.

162 **WARNINGS**

163 VELCADE should be administered under the supervision of a physician experienced in
164 the use of antineoplastic therapy.

165 ***Pregnancy Category D***

166

167 Women of childbearing potential should avoid becoming pregnant while being treated
168 with VELCADE.

169

170 Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and
171 rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m² in the rat and 0.05 mg/kg; 0.6
172 mg/m² in the rabbit) when administered during organogenesis. These dosages are
173 approximately half the clinical dose of 1.3 mg/m² based on body surface area.

174

175 Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6
176 mg/m²) experienced significant post-implantation loss and decreased number of live
177 fetuses. Live fetuses from these litters also showed significant decreases in fetal weight.
178 The dose is approximately 0.5 times the clinical dose of 1.3 mg/m² based on body surface
179 area.

180

181 No placental transfer studies have been conducted with bortezomib. There are no
182 adequate and well-controlled studies in pregnant women. If VELCADE is used during
183 pregnancy, or if the patient becomes pregnant while receiving this drug, the patient
184 should be apprised of the potential hazard to the fetus.

185

186 **PRECAUTIONS**

187 ***Peripheral Neuropathy:*** VELCADE treatment causes a peripheral neuropathy that is
188 predominantly sensory, although cases of mixed sensori-motor neuropathy have also
189 been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling
190 in the feet or hands) and/or signs of peripheral neuropathy may experience worsening
191 during treatment with VELCADE. Patients should be monitored for symptoms of

192 neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia,
193 discomfort or neuropathic pain. Patients experiencing new or worsening peripheral
194 neuropathy may require change in the dose and schedule of VELCADE (**see DOSAGE
195 AND ADMINISTRATION**). Limited follow-up data regarding the outcome of
196 peripheral neuropathy are available. Of the patients who experienced treatment emergent
197 neuropathy more than 70% had previously been treated with neurotoxic agents and more
198 than 80% of these patients had signs or symptoms of peripheral neuropathy at baseline
199 (**also see ADVERSE REACTIONS**).

200 **Hypotension:** VELCADE treatment can cause orthostatic/postural hypotension in about
201 12% of patients. These events are observed throughout therapy. Caution should be used
202 when treating patients with a history of syncope, patients receiving medications known to
203 be associated with hypotension, and patients who are dehydrated. Management of
204 orthostatic/postural hypotension may include adjustment of antihypertensive medications,
205 hydration, or administration of mineralocorticoids.

206
207 **Gastrointestinal Adverse Events:** VELCADE treatment can cause nausea, diarrhea,
208 constipation, and vomiting (**see ADVERSE REACTIONS**) sometimes requiring use of
209 antiemetics and antidiarrheals. Fluid and electrolyte replacement should be administered
210 to prevent dehydration.

211 **Thrombocytopenia:** Thrombocytopenia, which occurred in about 40% of patients
212 throughout therapy, was maximal at day 11 and usually recovered by the next cycle.
213 Complete blood counts including platelet counts should be frequently monitored
214 throughout treatment. Onset is most common in Cycles 1 and 2 but can continue
215 throughout therapy. There have been reports of gastrointestinal and intracerebral
216 hemorrhage in association with VELCADE induced thrombocytopenia. VELCADE
217 treatment may be temporarily discontinued if patients experience Grade 4
218 thrombocytopenia. VELCADE may be reinitiated at a reduced dose after resolution of
219 thrombocytopenia (**see DOSAGE AND ADMINISTRATION and ADVERSE
220 REACTIONS**).

221

222 ***Patients with Hepatic Impairment***

223 Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in
224 patients with hepatic impairment. These patients should be closely monitored for
225 toxicities when treated with VELCADE.

226 (**see CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations**)

227

228 ***Patients with Renal Impairment***

229

230 No clinical information is available on the use of VELCADE in patients with creatinine
231 clearance values less than 13 mL/min and patients on hemodialysis. These patients
232 should be closely monitored for toxicities when treated with VELCADE (**see
233 CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations**).

234

235 ***Animal Toxicity Findings***

236

237 *Cardiovascular toxicity*

238 Studies in monkeys showed that administration of dosages approximately twice the
239 recommended clinical dose resulted in heart rate elevations, followed by profound
240 progressive hypotension, bradycardia, and death 12-14 hours post dose. Doses
241 $\geq 1.2 \text{ mg/m}^2$ induced dose proportional changes in cardiac parameters. Bortezomib has
242 been shown to distribute to most tissues in the body, including the myocardium. In a
243 repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and
244 necrosis were also observed.

245

246 *Chronic Administration*

247 In animal studies at a dose and schedule similar to that recommended for patients (twice
248 weekly dosing for 2 weeks followed by 1 week rest) toxicities observed included severe
249 anemia and thrombocytopenia, gastrointestinal, neurological and lymphoid system
250 toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling
251 and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord.
252 Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were
253 observed.

254

255 *Information for Patients*

256 Physicians are advised to discuss the following with patients to whom VELCADE will be
257 administered.

258

259 *Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability:*

260 Since VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural
261 hypotension, diplopia or blurred vision, patients should be cautious when operating
262 machinery, including automobiles.

263

264 *Pregnancy/Nursing:* Patients should be advised to use effective contraceptive measures to
265 prevent pregnancy and to avoid breast feeding during treatment with VELCADE.

266

267 *Dehydration/Hypotension:* Since patients receiving VELCADE therapy may experience
268 vomiting and/or diarrhea, patients should be advised regarding appropriate measures to
269 avoid dehydration. Patients should be instructed to seek medical advice if they
270 experience symptoms of dizziness, light headedness or fainting spells.

271

272 *Concomitant Medications:* Patients should be cautioned about the use of concomitant
273 medications that may be associated with peripheral neuropathy (such as amiodarone, anti-
274 virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

275

276 *Peripheral Neuropathy:* Patients should be instructed to contact their physician if they
277 experience new or worsening symptoms of peripheral neuropathy (**see PRECAUTIONS**
278 **and DOSAGE AND ADMINISTRATION**).

279

280 ***Drug Interactions***

281 No formal drug interaction studies have been conducted with VELCADE.
282

283 *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate for
284 cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly
285 receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4
286 should be closely monitored for either toxicities or reduced efficacy (**see CLINICAL
287 PHARMACOLOGY/Pharmacokinetics-Drug Interactions**).
288

289 During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients
290 receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE
291 treatment may require close monitoring of their blood glucose levels and adjustment of
292 the dose of their antidiabetic medication.
293

294 ***Drug Laboratory Test Interactions***

295 None known.

296 ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

297 Carcinogenicity studies have not been conducted with bortezomib.
298

299 Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in*
300 *vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was
301 not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo*
302 micronucleus assay in mice.
303

304 Fertility studies with bortezomib were not performed but evaluation of reproductive
305 tissues has been performed in the general toxicity studies. In the 6-month rat toxicity
306 study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m² (one-fourth
307 of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2
308 mg/m². VELCADE could have a potential effect on either male or female fertility.
309

310 ***Pregnancy Category D (see WARNINGS)***

311

312 ***Nursing Mothers***

313 It is not known whether bortezomib is excreted in human milk. Because many drugs are
314 excreted in human milk and because of the potential for serious adverse reactions in
315 nursing infants from VELCADE, women should be advised against breast feeding while
316 being treated with VELCADE.

317 ***Pediatric Use***

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

319 *Geriatric Use*

320 Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%)
321 of patients aged 65 years or older experienced responses versus 32% in patients under the
322 age of 65. Across the 256 patients analyzed for safety, the incidence of Grade 3 or 4
323 events reported was 74%, 80%, and 85% for patients ≤ 50 years, 51 to 65 years, and >65
324 years, respectively.

325

326 **ADVERSE REACTIONS**

327 The two studies described (**see CLINICAL STUDIES**) evaluated 228 patients with
328 multiple myeloma receiving VELCADE 1.3 mg/m²/dose twice weekly for 2 weeks
329 followed by a 10-day rest period (21 day treatment cycle length) for a maximum of 8
330 treatment cycles.

331 The most commonly reported adverse events were asthenic conditions (including fatigue,
332 malaise and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased
333 (including anorexia) (43%), constipation (43%), thrombocytopenia (43%), peripheral
334 neuropathy (including peripheral sensory neuropathy and peripheral neuropathy
335 aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Fourteen percent
336 of patients experienced at least one episode of grade 4 toxicity, with the most common
337 toxicity being thrombocytopenia (3%) and neutropenia (3%).

338

339 ***Serious Adverse Events (SAEs):*** Serious Adverse Events are defined as any event,
340 regardless of causality, that: results in death, is life-threatening, requires hospitalization
341 or prolongs a current hospitalization, results in a significant disability or is deemed to be
342 an important medical event. A total of 113 (50%) of the 228 patients experienced SAEs
343 during the studies. The most commonly reported SAEs included pyrexia (7%),
344 pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

345

346 Adverse events thought by the investigator to be drug-related and leading to
347 discontinuation occurred in 18% of patients. The reasons for discontinuation included
348 peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

349

350 Two deaths were reported and considered by the investigator to be possibly related to
351 study drug: one case of cardiopulmonary arrest and one case of respiratory failure.

352

353 The most common adverse events are shown in **Table 3**. All adverse events occurring at
354 $\geq 10\%$ are included. In the single arm studies conducted it is often not possible to
355 distinguish adverse events that are drug-caused and those that reflect the patient's
356 underlying disease. See discussion of specific adverse reactions following **Table 3**.

Table 3: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events (N = 228)

Adverse Event	All Patients (N = 228) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events
Asthenic conditions	149 (65)	42 (18)	1 (<1)
Nausea	145 (64)	13 (6)	0
Diarrhea	116 (51)	16 (7)	2 (<1)
Appetite decreased	99 (43)	6 (3)	0
Constipation	97 (43)	5 (2)	0
Thrombocytopenia	97 (43)	61 (27)	7 (3)
Peripheral neuropathy	84 (37)	31 (14)	0
Pyrexia	82 (36)	9 (4)	0
Vomiting	82 (36)	16 (7)	1 (<1)
Anemia	74 (32)	21 (9)	0
Headache	63 (28)	8 (4)	0
Insomnia	62 (27)	3 (1)	0
Arthralgia	60 (26)	11 (5)	0
Pain in limb	59 (26)	16 (7)	0
Edema	58 (25)	3 (1)	0
Neutropenia	55 (24)	30 (13)	6 (3)
Paresthesia and dysesthesia	53 (23)	6 (3)	0
Dyspnea	50 (22)	7 (3)	1 (<1)
Dizziness (excluding vertigo)	48 (21)	3 (1)	0
Rash	47 (21)	1 (<1)	0
Dehydration	42 (18)	15 (7)	0
Upper respiratory tract infection	41 (18)	0	0
Cough	39 (17)	1 (<1)	0
Bone pain	33 (14)	5 (2)	0
Anxiety	32 (14)	0	0
Myalgia	32 (14)	5 (2)	0
Back pain	31 (14)	9 (4)	0
Muscle cramps	31 (14)	1 (<1)	0
Dyspepsia	30 (13)	0	0
Abdominal pain	29 (13)	5 (2)	0
Dysgeusia	29 (13)	1 (<1)	0
Hypotension	27 (12)	8 (4)	0
Rigors	27 (12)	1 (<1)	0
Herpes zoster	26 (11)	2 (<1)	0
Pruritus	26 (11)	0	0
Vision blurred	25 (11)	1 (<1)	0
Pneumonia	23 (10)	12 (5)	0

358 ***Asthenic conditions (fatigue, malaise, weakness)***

359

360 Asthenia was reported in 65% of patients and was predominantly reported as Grade 1 or
361 2. The first onset of fatigue was most often reported during the 1st and 2nd cycles of
362 therapy. Asthenia was Grade 3 for 18% of patients. Two percent of patients
363 discontinued treatment due to fatigue.

364

365 ***Gastrointestinal Events***

366

367 The majority of patients experienced gastrointestinal adverse events during the studies,
368 including nausea, diarrhea, constipation, and vomiting. Grade 3 or 4 gastrointestinal
369 events occurred in 21% of patients and were considered serious in 13% of patients.
370 Vomiting and diarrhea each were of Grade 3 severity in 7% of patients and were Grade 4
371 in <1%. Five percent of patients discontinued due to gastrointestinal events. Appetite
372 decreased (anorexia) was reported as an adverse event for 43% of patients. The
373 incidence of Grade 3 decreased appetite was 3%.

374

375 ***Thrombocytopenia***

376

377 Thrombocytopenia was reported during treatment with VELCADE for 43% of patients.
378 The thrombocytopenia was characterized by a dose related decrease in platelet count
379 during the VELCADE dosing period (days 1 to 11) with a return to baseline in platelet
380 count during the rest period (days 12 to 21) in each treatment cycle. Thrombocytopenia
381 was Grade 3 or 4 in intensity for 27% and 3% respectively of patients. Four percent (4%)
382 of patients discontinued VELCADE treatment due to thrombocytopenia of any grade.

383

384 ***Peripheral Sensory Neuropathy***

385

386 Events reported as peripheral neuropathy, peripheral sensory neuropathy, and peripheral
387 neuropathy aggravated occurred in 37% of patients. Peripheral neuropathy was Grade 3
388 for 14% of patients with no Grade 4 events. New onset or worsening of existing
389 neuropathy was noted throughout the cycles of treatment. Six percent (6%) of patients
390 discontinued VELCADE due to neuropathy. More than 80% of all study patients had
391 signs or symptoms of peripheral neuropathy at baseline evaluation. The incidence of
392 Grade 3 neuropathy was 5% (2 of 41 patients) in patients without baseline neuropathy.
393 Symptoms may improve or return to baseline in some patients upon discontinuation of
394 VELCADE. The complete time-course of this toxicity has not been fully characterized.

395

396 ***Pyrexia***

397

398 Pyrexia (>38°C) was reported as an adverse event for 36% of patients and was assessed
399 as Grade 3 in 4% of patients.

400 ***Neutropenia***

401 Neutropenia occurred in 24% of patients and was grade 3 in 13% and grade 4 in 3%.
402 The incidence of febrile neutropenia was <1%.

403

404 ***Hypotension***

405

406 Hypotension (including reports of orthostatic hypotension) was reported in 12% of
407 patients. Most events were Grade 1 or 2 in severity. Grade 3 hypotension occurred in
408 4% of patients; no patient experienced Grade 4 hypotension. Patients developing
409 orthostatic hypotension did not have evidence of orthostatic hypotension at study entry;
410 half had pre-existing hypertension and one third had evidence of peripheral neuropathy.
411 Doses of antihypertensive medications may need to be adjusted in patients receiving
412 VELCADE. Four percent of patients experienced hypotension, including orthostatic
413 hypotension, and had a concurrent syncopal event.

414

415 ***Serious Adverse Events from Clinical Studies***

416

417 In approximately 580 patients, the following serious adverse events (not described above)
418 were reported, considered at least possibly related to study medication, in at least one
419 patient treated with VELCADE administered as monotherapy or in combination with
420 other chemotherapeutics. These studies were conducted in patients with hematological
421 malignancies and in solid tumors.

422

423 ***Blood and lymphatic system disorders:*** Disseminated intravascular coagulation

424

425 ***Cardiac disorders:*** Atrial fibrillation aggravated, atrial flutter, cardiac amyloidosis,
426 cardiac arrest, cardiac failure congestive, myocardial ischemia, myocardial infarction,
427 pericardial effusion, pulmonary edema, ventricular tachycardia

428

429 ***Gastrointestinal disorders:*** Ascites, dysphagia, fecal impaction, gastritis hemorrhagic,
430 gastrointestinal hemorrhage, hematemesis, ileus paralytic, large intestinal obstruction,
431 paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation,
432 stomatitis, melena, pancreatitis acute

433

434 ***Hepatobiliary:*** Hyperbilirubinemia, portal vein thrombosis

435

436 ***Immune system disorders:*** Anaphylactic reaction, drug hypersensitivity, immune
437 complex mediated hypersensitivity

438

439 ***Infections and Infestations:*** Bacteremia

440

441 ***Injury, poisoning and procedural complications:*** Skeletal fracture, subdural hematoma

442

443 ***Metabolism and nutrition disorders:*** Hypocalcemia, hyperuricemia, hypokalemia,
444 hyponatremia, tumor lysis syndrome

445 ***Nervous system:*** Ataxia, coma, dizziness, dysarthria, dysautonomia, cranial palsy, grand
446 mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression,
447 transient ischemic attack

448

449 ***Psychiatric:*** Agitation, confusion, psychotic disorder, suicidal ideation

450

451 ***Renal and urinary:*** Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria
452 urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular
453 nephritis proliferative

454

455 ***Respiratory, thoracic and mediastinal:*** Acute respiratory distress syndrome, atelectasis,
456 chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional,
457 epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis,
458 respiratory distress, respiratory failure

459

460 ***Vascular:*** Cerebrovascular accident, deep venous thrombosis, peripheral embolism,
461 pulmonary embolism

462 **OVERDOSAGE**

463 Cardiovascular safety pharmacology studies in monkeys show that lethal IV doses are
464 associated with decreases in blood pressure, increases in heart rate, increases in
465 contractility, and ultimately terminal hypotension. In monkeys, doses of 3.0 mg/m² and
466 greater (approximately twice the recommended clinical dose) resulted in progressive
467 hypotension starting at 1 hour and progressing to death by 12 to 14 hours following drug
468 administration.

469

470 No cases of overdosage with VELCADE were reported during clinical trials. Single
471 doses of up to 2.0 mg/m² per week have been administered in adults. In the event of
472 overdosage, patient's vital signs should be monitored and appropriate supportive care
473 given to maintain blood pressure and body temperature (**see PRECAUTIONS and**
474 **DOSAGE AND ADMINISTRATION**).

475

476 There is no known specific antidote for VELCADE overdosage.

477 **DOSAGE AND ADMINISTRATION**

478 The recommended dose of VELCADE is 1.3 mg/m²/dose administered as a bolus
479 intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-
480 day rest period (days 12-21) (**see CLINICAL STUDIES section for a description of**
481 **dose administration during the trials**).

482

483 This 3-week period is considered a treatment cycle. At least 72 hours should elapse
484 between consecutive doses of VELCADE.

485

486 ***Dose Modification and Reinitiation of Therapy***

487

488 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or
 489 Grade 4 hematological toxicities excluding neuropathy as discussed below (see
 490 **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE
 491 therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0
 492 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose). The following table contains
 493 the recommended dose modification for the management of patients who experience
 494 VELCADE-related neuropathic pain and/or peripheral sensory neuropathy (**Table 4**).
 495 Patients with pre-existing severe neuropathy should be treated with VELCADE only after
 496 careful risk/benefit assessment.

497 **Table 4: Recommended Dose Modification for VELCADE-related Neuropathic Pain**
 498 **and/or Peripheral Sensory Neuropathy**

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
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 VELCADE to 1.0 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m ² and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue VELCADE

499 NCI Common Toxicity Criteria website – <http://ctep.info.nih.gov/reporting/ctc.html>

500

501 **Administration Precautions:** VELCADE is an antineoplastic. Caution should be used
 502 during handling and preparation. Proper aseptic technique should be used. Use of gloves
 503 and other protective clothing to prevent skin contact is recommended. In clinical trials,
 504 local skin irritation was reported in 5% of patients, but extravasation of VELCADE was
 505 not associated with tissue damage.

506

507 **Reconstitution/Preparation for Intravenous Administration:** Prior to use, the contents
 508 of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride
 509 Injection, USP. The reconstituted product should be a clear and colorless solution.

510

511 Parenteral drug products should be inspected visually for particulate matter and
 512 discoloration prior to administration whenever solution and container permit. If any
 513 discoloration or particulate matter is observed, the reconstituted product should not be
 514 used.

515

516 **Stability:** Unopened vials of VELCADE are stable until the date indicated on the package
 517 when stored in the original package protected from light.

518

519 VELCADE contains no antimicrobial preservative. When reconstituted as directed,
520 VELCADE may be stored at 25°C (77°F); excursions permitted from 15 to 30°C (59 to
521 86°F) [see USP Controlled Room Temperature]. Reconstituted VELCADE should be
522 administered within eight hours of preparation. The reconstituted material may be stored
523 in the original vial and/or the syringe prior to administration. The product may be stored
524 for up to three hours in a syringe, however total storage time for the reconstituted
525 material must not exceed eight hours when exposed to normal indoor lighting.

526

527 **HOW SUPPLIED**

528

529 VELCADE (bortezomib) for Injection is supplied as individually cartoned 10 mL vials
530 containing 3.5 mg of bortezomib as a white to off-white cake or powder.

531

532 NDC 63020-049-01

533 3.5 mg single dose vial

534

535 **STORAGE**

536

537 Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions
538 permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Retain
539 in original package to protect from light.

540

541 **Caution:** Rx only

542

543 U.S. Patents: 5,780,454; 6,083,903; 6,297,217

544

545 **Distributed and Marketed by:**

546 Millennium Pharmaceuticals, Inc.

547 75 Sidney St.

548 Cambridge, MA 02139

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555 **References:** **1.** Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G et al.
556 Criteria for evaluating disease response and progression in patients with multiple myeloma
557 treated by high- dose therapy and haematopoietic stem cell transplantation. Myeloma
558 Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *British Journal*
559 *of Haematology* 1998;102(5):1115-1123. **2.** Salmon SE, Haut A, Bonnet JD, Amare M, Weick
560 JK, Durie BG et al. Alternating combination chemotherapy and levamisole improves survival in
561 multiple myeloma: a Southwest Oncology Group Study. *Journal of Clinical Oncology* 1983;1(8):
562 453-461.
563

564 **VELCADE™ (bortezomib) for Injection**

565

566 **PATIENT INFORMATION**

567

568 VELCADE is intended for use under the guidance and supervision of a health care
569 professional. Please discuss the possibility of the following side effects with your doctor:

570

571 ***Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability:***

572 VELCADE may be associated with fatigue, dizziness, light-headedness, fainting or
573 blurred vision. Please exercise caution or avoid operating machinery, including
574 automobiles, following use of VELCADE.

575

576 ***Pregnancy/Nursing:*** Please use effective contraceptive measures to prevent pregnancy
577 and avoid breast feeding during treatment with VELCADE.

578

579 ***Dehydration/Hypotension:*** Following the use of VELCADE therapy, you may
580 experience vomiting and/or diarrhea. Drink plenty of fluids. Speak with your doctor if
581 these symptoms occur about what you should do to control or manage these symptoms.

582

583 If you experience symptoms of dizziness or light-headedness, consult a healthcare
584 professional. Seek immediate medical attention if you experience fainting spells.

585

586 ***Concomitant Medications:*** Please speak with your doctor about any other medication
587 you are currently taking. Your doctor will want to be aware of any other medications.

588

589 ***Peripheral Neuropathy:*** Contact your doctor if you experience new or worsening
590 symptoms of peripheral neuropathy such as numbness, pain, or a burning feeling in the
591 feet or hands.

592

593

594

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