

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

2 **PRESCRIBING INFORMATION**

3 **DESCRIPTION**

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

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

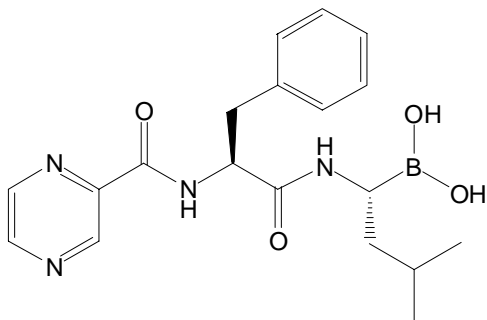
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14 The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-
15 oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

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17 Bortezomib has the following chemical structure:

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

24 **CLINICAL PHARMACOLOGY**

25 ***Mechanism of Action***

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

33 types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models,
34 including multiple myeloma.

35

36 ***Pharmacokinetics***

37 Following intravenous administration of a 1.3 mg/m² dose, the median estimated maximum
38 plasma concentration of bortezomib was 509 ng/mL (range=109 to 1300 ng/mL) in 8 patients
39 with multiple myeloma and creatinine clearance values ranging from 31 to 169 mL/min. The
40 mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses
41 ranging from 1.45 to 2.00 mg/m² in patients with advanced malignancies. The pharmacokinetics
42 of bortezomib as a single agent have not been fully characterized at the recommended dose in
43 multiple myeloma patients.

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45 ***Distribution***

46

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

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51 ***Metabolism***

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

61 ***Elimination***

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

64

65 ***Special Populations***

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

69

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

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73 ***Renal Impairment:*** No pharmacokinetic studies were conducted with bortezomib in patients
74 with renal impairment. Clinical studies included patients with creatinine clearance values as low
75 as 13.8 mL/min (see **PRECAUTIONS**).

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

78

79 ***Drug Interactions***

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

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

83 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and
84 3A4, with IC₅₀ values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC₅₀ =
85 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

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

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90 **CLINICAL STUDIES**

91 ***Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma***

92 A prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial
93 enrolling 669 patients was designed to determine whether VELCADE resulted in improvement
94 in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive
95 multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior
96 high-dose dexamethasone were excluded as were those with baseline grade ≥ 2 peripheral
97 neuropathy or platelet counts < 50, 000/μL. A total of 627 patients were evaluable for response.

98 Stratification factors were based on the number of lines of prior therapy the patient had
99 previously received (1 previous line versus more than 1 line of therapy), time of progression
100 relative to prior treatment (progression during or within 6 months of stopping their most recent
101 therapy versus relapse >6 months after receiving their most recent therapy), and screening
102 β₂-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).

103 Baseline patient and disease characteristics are summarized in **Table 1**.

Table 1: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial

Patient Characteristics	VELCADE N=333	Dexamethasone N=336
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤ 70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10 ⁹ /L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β_2 -microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤ 30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)		
	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
> 1 prior line	60%	65%
All Patients		
	(N=333)	(N=336)
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

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106 Patients in the VELCADE treatment group were to receive eight 3-week treatment cycles
 107 followed by three 5-week treatment cycles of VELCADE. Within each 3-week treatment cycle,
 108 VELCADE 1.3 mg/m²/dose alone was administered by IV bolus twice weekly for 2 weeks on
 109 Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week
 110 treatment cycle, VELCADE 1.3 mg/m²/dose alone was administered by IV bolus once weekly
 111 for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35) (see
 112 **DOSAGE AND ADMINISTRATION**).

113 Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles
 114 followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone
 115 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a
 116 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone 40
 117 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5
 118 to 28). Patients with documented progressive disease on dexamethasone were offered
 119 VELCADE at a standard dose and schedule on a companion study.

120 Following a preplanned interim analysis of time to progression, the dexamethasone arm was
 121 halted and all patients randomized to dexamethasone were offered VELCADE, regardless of

122 disease status. At this time of study termination, a final statistical analysis was performed. Due
123 to this early termination of the study, the median duration of follow-up for surviving patients
124 (n=534) is limited to 8.3 months.

125 In the VELCADE arm, 34% of patients received at least one VELCADE dose in all 8 of the 3-
126 week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number
127 of VELCADE doses during the study was 22, with a range of 1 to 44. In the dexamethasone
128 arm, 40% of patients received at least one dose in all 4 of the 5-week treatment cycles of therapy,
129 and 6% received at least one dose in all 9 cycles.

130 The time to event analyses and response rates from the phase 3 trial are presented in **Table 2**.
131 Response and progression were assessed using the European Group for Blood and Marrow
132 Transplantation (EBMT) criteria.¹ Complete response (CR) required < 5% plasma cells in the
133 marrow, 100% reduction in M-protein, and a negative immunofixation test (IF⁻). Partial
134 Response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine
135 myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable
136 bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the
137 criteria for complete response including 100% reduction in M-protein by protein electrophoresis,
138 however M-protein was still detectable by immunofixation (IF⁺).
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Table 2: Summary of Efficacy Analyses in the Randomized Phase 3 Study

	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE n=333	Dex n=336	VELCADE n=132	Dex n=119	VELCADE n=200	Dex n=217
Efficacy Endpoint						
Time to Progression –						
Events n (%)	147(44)	196(58)	55(42)	64(54)	92(46)	132(61)
Median ^a (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (2.8, 3.5)
Hazard ratio ^b (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value ^c	< 0.0001		0.0019		<0.0001	
Overall Survival						
Events (deaths) n (%)	51(15)	84(25)	12(9)	24(20)	39(20)	60(28)
Hazard ratio ^b (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value ^{c,d}	<0.05		<0.05		<0.05	
Response Rate						
population ^e n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR ^f n (%)	20(6)	2(<1)	8(6)	2(2)	12(6)	0(0)
PR ^f n(%)	101(32)	54(17)	49(38)	27(25)	52(28)	27(13)
nCR ^{f,g} n(%)	21(7)	3(<1)	8(6)	2(2)	13(7)	1(<1)
CR + PR ^f n (%)	121 (38)	56 (18)	57(45)	29(26)	64(34)	27(13)
p-value ^h	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR ^f	9.9 mo	NE ⁱ	9.9 mo	NE	6.3 mo	NA ^j
nCR ^f	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR ^f	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

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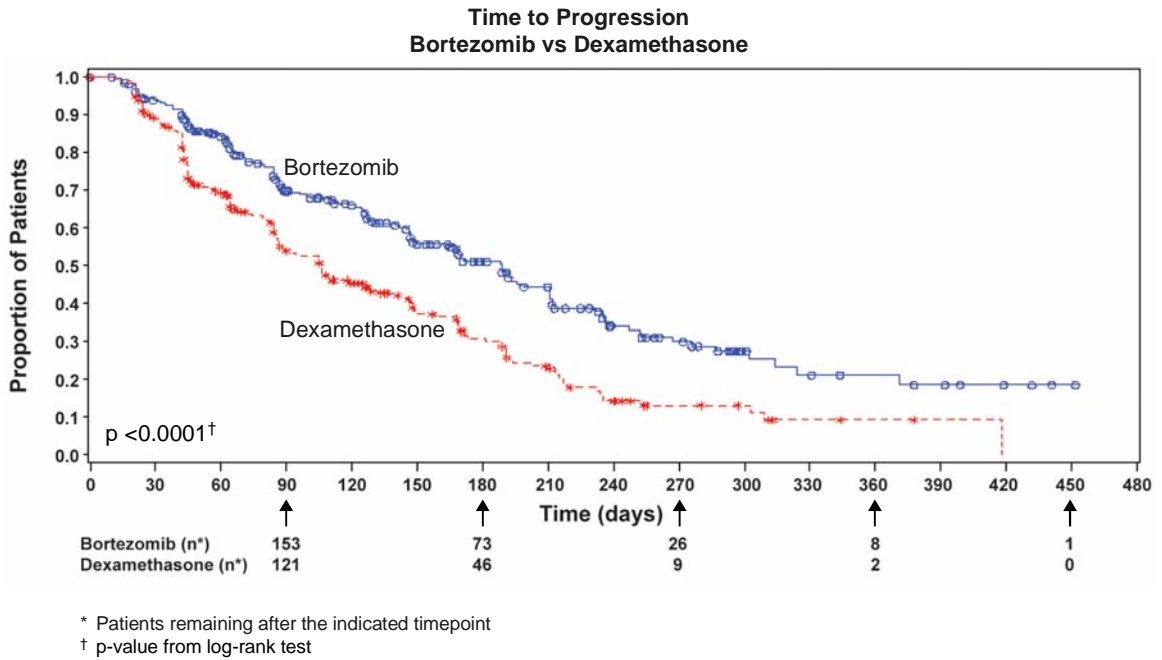
^a Kaplan-Meier estimate.
^b Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for VELCADE.
^c p-value based on the stratified log-rank test including randomization stratification factors.
^d Precise p-value cannot be rendered
^e Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.
^f EBMT criteria¹; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria. nCR is in the PR category.
^g In 2 patients the IF was unknown.
^h p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors;
ⁱ Not Estimable.
^j Not Applicable, no patients in category.

165 TTP was statistically significantly longer on the VELCADE arm (see Fig. 1).

166 Figure 1: Time to Progression

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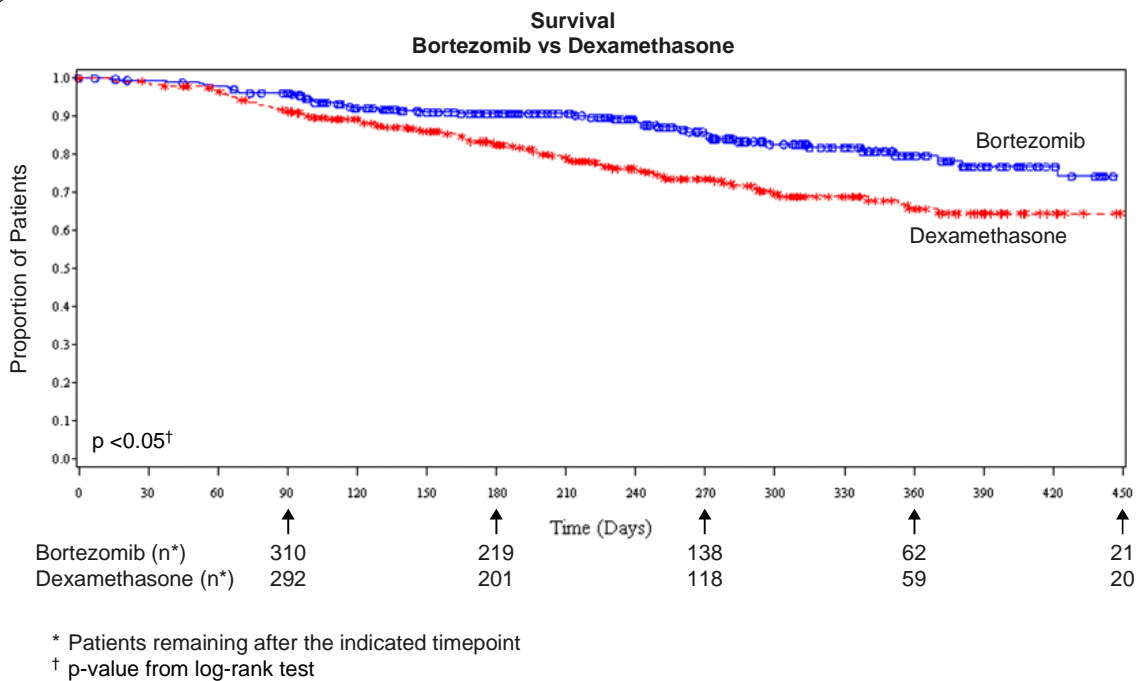
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181 As shown in Figure 2, VELCADE had a significant survival advantage relative to
182 dexamethasone ($p < 0.05$). The median follow-up was 8.3 months.

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184 Figure 2: Overall Survival

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198 For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median
199 duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI:
200 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was
201 significantly higher on the VELCADE arm regardless of β_2 -microglobulin levels at
202 baseline.

203

204 *Phase 2 Single-arm Clinical Study in Relapsed Multiple Myeloma*

205

206 The safety and efficacy of VELCADE in relapsed multiple myeloma were evaluated in
207 an open-label, single-arm, multicenter study of 202 patients who had received at least 2
208 prior therapies and demonstrated disease progression on their most recent therapy. The
209 median number of prior therapies was 6. Baseline patient and disease characteristics are
210 summarized in **Table 3**.

211

212 An IV bolus injection of VELCADE 1.3 mg/m²/dose was administered twice weekly for
213 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a
214 maximum of 8 treatment cycles. The study employed dose modifications for toxicity (**see**
215 **DOSAGE AND ADMINISTRATION**). Patients who experienced a response to
216 VELCADE were allowed to continue VELCADE treatment in an extension study.

217 **Table 3: Summary of Baseline Patient and Disease Characteristics in a Single-arm**
 218 **Phase 2 Study***
 219

	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%

220 * Based on number of patients with baseline data available

221

222 Responses to VELCADE alone are shown in **Table 4**. Response rates to VELCADE
 223 alone were determined by an independent review committee (IRC) based on EBMT
 224 criteria.¹ Response rates using the Southwest Oncology Group (SWOG) criteria² are also
 225 shown. SWOG response required a $\geq 75\%$ reduction in serum myeloma protein and/or
 226 $\geq 90\%$ urine protein. A total of 188 patients were evaluable for response; 9 patients with
 227 nonmeasurable disease could not be evaluated for response by the IRC, and 5 patients
 228 were excluded from the efficacy analyses because they had had minimal prior therapy.
 229 The mean number of cycles administered was 6. The median time to response was 38
 230 days (range 30 to 127 days). The median survival of all patients enrolled was 17 months
 231 (range <1 to 36+ months).

232 **Table 4: Summary of Disease Outcomes (Phase 2 study)**

Response Analyses (VELCADE monotherapy)	N = 188	N (%)	(95% CI)
Overall Response Rate (EBMT) (CR + PR)		52 (28%)	(21, 35)
Complete Response (CR)		5 (3%)	(1, 6)
Partial Response (PR)		47 (25%)	(19, 32)
Clinical Remission (SWOG) ^a		33 (18%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)		385 Days	(245, 538)

233 ^a **Clinical Remission (SWOG)** required $\geq 75\%$ reduction in serum myeloma protein and/or $\geq 90\%$ reduction
 234 of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease
 235 and normal calcium.²

236 Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%)
 237 of patients aged 65 years or older experienced CR or PR.

238 In this study, the response rate to VELCADE, based on a univariate analysis, was
 239 independent of the number and types of prior therapies. There was a decreased
 240 likelihood of response in patients with either $>50\%$ plasma cells or abnormal cytogenetics
 241 in the bone marrow. Responses were seen in patients with chromosome 13
 242 abnormalities.

243 *A Randomized Phase 2 Dose-Response Study in Relapsed Multiple Myeloma*

244 An open-label, multicenter study randomized 54 patients with multiple myeloma who had
 245 progressed or relapsed on or after front-line therapy to receive VELCADE 1.0 mg/m² or
 246 1.3 mg/m² IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-
 247 day rest period (Days 12 to 21). The median duration of time between diagnosis of
 248 multiple myeloma and first dose of VELCADE on this trial was 2.0 years, and patients
 249 had received a median of 1 prior line of treatment (median of 3 prior therapies). A single
 250 complete response was seen at each dose. The overall response rates (CR + PR) were
 251 30% (8/27) at 1.0 mg/m² and 38% (10/26) at 1.3 mg/m².

252 *A Phase 2 Open-Label Extension Study*

253 Patients from the two phase 2 studies who in the investigators' opinion would experience
 254 additional clinical benefit continued to receive VELCADE beyond 8 cycles on an
 255 extension study. Sixty-three (63) patients from the phase 2 multiple myeloma studies
 256 were enrolled and received a median of 7 additional cycles of VELCADE therapy for a
 257 total median of 14 cycles (range 7 to 32). The overall median dosing intensity was the
 258 same in both the parent protocol and extension study. Sixty-seven percent (67%) of
 259 patients initiated the extension study at the same or higher dose intensity at which they
 260 completed the parent protocol, and 89% of patients maintained the standard 3-week
 261 dosing schedule during the extension study. No new cumulative or new long-term
 262 toxicities were observed with prolonged VELCADE treatment (**see ADVERSE**
 263 **EVENTS**).

264

265 **INDICATIONS AND USAGE**

266 VELCADE[®] (bortezomib) for Injection is indicated for the treatment of multiple
267 myeloma patients who have received at least 1 prior therapy.

268 **CONTRAINDICATIONS**

269 VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or
270 mannitol.

271 **WARNINGS**

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

274 ***Pregnancy Category D***

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276 Women of childbearing potential should avoid becoming pregnant while being treated
277 with VELCADE.

278

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

283

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

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

293 **PRECAUTIONS**

294 ***Peripheral Neuropathy:*** VELCADE treatment causes a peripheral neuropathy that is
295 predominantly sensory, although cases of motor neuropathy have also been reported.
296 Patients with preexisting symptoms (numbness, pain or a burning feeling in the feet or
297 hands) and/or signs of peripheral neuropathy may experience worsening peripheral
298 neuropathy (including ≥ Grade 3) during treatment with VELCADE. Patients should be
299 monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia,
300 hypoesthesia, paresthesia, discomfort or neuropathic pain. Patients experiencing new or
301 worsening peripheral neuropathy may require changes in the dose and schedule of
302 VELCADE (see **DOSAGE AND ADMINISTRATION**). Following dose adjustments,
303 improvement in or resolution of peripheral neuropathy was reported in 51% of patients

304 with \geq Grade 2 peripheral neuropathy in phase 3 study. Improvement in or resolution of
305 peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2
306 neuropathy or who had \geq Grade 3 peripheral neuropathy in the phase 2 studies (**also see**
307 **ADVERSE REACTIONS**).

308 **Hypotension:** In phase 2 and 3 studies, the incidence of hypotension (postural,
309 orthostatic, and hypotension NOS) was 11% to 12%. These events are observed
310 throughout therapy. Caution should be used when treating patients with a history of
311 syncope, patients receiving medications known to be associated with hypotension, and
312 patients who are dehydrated. Management of orthostatic/postural hypotension may
313 include adjustment of antihypertensive medications, hydration, and administration of
314 mineralocorticoids and/or sympathomimetics (**see ADVERSE REACTIONS**).

315 **Cardiac Disorders:** The acute development or exacerbation of congestive heart failure
316 has been seen in patients with risk factors for, or existing heart disease. Such patients
317 should be closely monitored. In the phase 3 study, the incidence of any treatment-
318 emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone
319 groups, respectively. The incidence of heart failure events (acute pulmonary edema,
320 cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was
321 similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There
322 have been isolated cases of QT-interval prolongation in clinical studies; causality has not
323 been established.

324
325 **Laboratory Tests:** Complete blood counts (CBC) should be frequently monitored
326 throughout treatment with VELCADE.

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328 **Gastrointestinal Adverse Events:** VELCADE treatment can cause nausea, diarrhea,
329 constipation, and vomiting (**see ADVERSE REACTIONS**) sometimes requiring use of
330 antiemetic and antidiarrheal medications. Fluid and electrolyte replacement should be
331 administered to prevent dehydration.

332 **Thrombocytopenia:** VELCADE is associated with thrombocytopenia (**see ADVERSE**
333 **EVENTS**). Platelets were lowest at Day 11 of each cycle of VELCADE treatment and
334 typically recovered to baseline by the next cycle. The cyclical pattern of platelet count
335 decrease and recovery remained consistent over the 8 cycles of twice weekly dosing, and
336 there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir
337 measured was approximately 40% of baseline. The severity of thrombocytopenia related
338 to pretreatment platelet count is shown in **Table 5** for the phase 3 study. In the phase 3
339 study, the incidence of significant bleeding events (\geq Grade 3) was similar on both the
340 VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored
341 prior to each dose of VELCADE. VELCADE therapy should be held when the platelet
342 count is $<25,000/\mu\text{L}$ and reinitiated at a reduced dose (**see DOSAGE AND**
343 **ADMINISTRATION and ADVERSE REACTIONS**). There have been reports of
344 gastrointestinal and intracerebral hemorrhage in association with VELCADE.
345 Transfusions may be considered.

346 **Table 5: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the**
 347 **Phase 3 Study**

Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count <10,000/ μ L	Number (%) of Patients with Platelet Count 10,000-25,000/ μ L
$\geq 75,000/\mu$ L	309	8 (3%)	36 (12%)
$\geq 50,000/\mu$ L- <75,000/ μ L	14	2 (14%)	11 (79%)
$\geq 10,000/\mu$ L- <50,000/ μ L	7	1 (14%)	5 (71%)

348 * A baseline platelet count of 50,000/uL was required for study eligibility.

349 **Data were missing at baseline for 1 patient.

350 Thrombocytopenia was reported in 43% of patients in the phase 2 studies.

351

352 **Tumor Lysis Syndrome:** Because VELCADE is a cytotoxic agent and can rapidly kill
 353 malignant cells, the complications of tumor lysis syndrome may occur. Patients at risk of
 354 tumor lysis syndrome are those with high tumor burden prior to treatment. These patients
 355 should be monitored closely and appropriate precautions taken.

356

357 **Patients with Hepatic Impairment:** Bortezomib is metabolized by liver enzymes and
 358 bortezomib's clearance may decrease in patients with hepatic impairment. These patients
 359 should be closely monitored for toxicities when treated with VELCADE (see
 360 **CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations**).

361

362 **Patients with Renal Impairment:** No clinical information is available on the use of
 363 VELCADE in patients with creatinine clearance values less than 13 mL/min and patients
 364 on hemodialysis. Patients with renal impairment should be closely monitored for
 365 toxicities when treated with VELCADE (see **CLINICAL**
 366 **PHARMACOLOGY/Pharmacokinetics-Special Populations**).

367

368 *Animal Toxicity Findings*

369

370 *Cardiovascular toxicity*

371 Studies in monkeys showed that administration of dosages approximately twice the
 372 recommended clinical dose resulted in heart rate elevations, followed by profound
 373 progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses
 374 $\geq 1.2 \text{ mg/m}^2$ induced dose-proportional changes in cardiac parameters. Bortezomib has
 375 been shown to distribute to most tissues in the body, including the myocardium. In a
 376 repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and
 377 necrosis were also observed.

378 *Chronic Administration*

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

386

387 **Information for Patients**

388 Physicians are advised to discuss the PATIENT INFORMATION section with patients
389 prior to treatment with VELCADE (see **PATIENT INFORMATION**).

390

391 *Ability to Drive or Operate Machinery or Impairment of Mental Ability:*

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

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

399

400 **Drug Interactions**

401 No formal drug interaction studies have been conducted with VELCADE.

402

403 *In vitro* studies with human liver microsomes indicate that bortezomib is primarily a
404 substrate for cytochrome P450 3A4, 2C19, and 1A2. Patients who are concomitantly
405 receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4
406 should be closely monitored for either toxicities or reduced efficacy (see **CLINICAL
407 PHARMACOLOGY/Pharmacokinetics-Drug Interactions**).

408

409 During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients
410 receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE
411 treatment may require close monitoring of their blood glucose levels and adjustment of
412 the dose of their antidiabetic medication.

413

414 **Drug Laboratory Test Interactions**

415 None known.

416 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

417 Carcinogenicity studies have not been conducted with bortezomib.

418

419 Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in*
420 *vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was
421 not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo*
422 micronucleus assay in mice.

423

424 Fertility studies with bortezomib were not performed but evaluation of reproductive
425 tissues has been performed in the general toxicity studies. In the 6-month rat toxicity
426 study, degenerative effects in the ovary were observed at doses $\geq 0.3 \text{ mg/m}^2$ (one-fourth
427 of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2
428 mg/m^2 . VELCADE could have a potential effect on either male or female fertility.

429

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

431 **Pregnancy/Nursing:** Patients should be advised to use effective contraceptive measures to
432 prevent pregnancy.

433 *Nursing Mothers*

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

438 *Pediatric Use*

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

440 **Geriatric Use**

441 Of the 669 patients enrolled, 245 (37%) were 65 years of age or older: 125 (38%) on the
442 VELCADE arm and 120 (36%) on dexamethasone arm. Median time to progression and
443 median duration of response for patients ≥ 65 were longer on VELCADE compared to
444 dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the
445 VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response
446 (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4
447 events was 64%, 78% and 75% for VELCADE patients ≤ 50 , 51-64 and ≥ 65 years old,
448 respectively (see CLINICAL STUDIES).

449

450 In the phase 2 clinical study of 202 patients, 35% of patients were 65 years of age or
451 older, the incidence of Grade ≥ 3 events was 74%, 80%, and 85% for VELCADE patients
452 ≤ 50 , 51 to 65, and > 65 years old, respectively (see CLINICAL STUDIES).

453

454 No overall differences in safety or effectiveness were observed between patients \geq age 65
455 and younger patients receiving VELCADE; but greater sensitivity of some older
456 individuals cannot be ruled out.

457

458 **ADVERSE REACTIONS**

459 **Randomized Open-Label Phase 3 Clinical Study**

460 Among the 331 VELCADE treated patients, the most commonly reported events overall
461 were asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%),
462 peripheral neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia,, and
463 psychiatric disorders (each 35%), anorexia and appetite decreased (34%), paresthesia and
464 dysesthesia (27%),, anemia and headache (each 26%), and cough (21%). The most
465 commonly reported adverse events reported among the 332 patients in the
466 dexamethasone group were psychiatric disorders (49%), asthenic conditions (45%),
467 insomnia (27%), anemia (22%) and diarrhea and lower respiratory/lung infections (each
468 21%). Fourteen percent (14%) of patients in the VELCADE treated arm experienced a
469 Grade 4 adverse event; the most common toxicities were thrombocytopenia (4%),
470 neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%) of dexamethasone
471 treated patients experienced a Grade 4 adverse event; the most common toxicity was
472 hyperglycemia (2%).

473 **Serious Adverse Events (SAEs)**

474 Serious adverse events are defined as any event, regardless of causality, that results in
475 death, is life-threatening, requires hospitalization or prolongs a current hospitalization,
476 results in a significant disability, or is deemed to be an important medical event. A total
477 of 144 (44%) patients from the VELCADE treatment arm experienced an SAE during the
478 study, as did 144 (43%) dexamethasone-treated patients. The most commonly reported
479 SAEs in the VELCADE treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and
480 pneumonia (4%), and vomiting (3%). In the dexamethasone treatment group, the most
481 commonly reported SAEs were pneumonia (7%), pyrexia (4%), and hyperglycemia (3%).

482 A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment
483 group and 61 (18%) of 332 patients in the dexamethasone treatment group were
484 discontinued from treatment due to adverse events assessed as drug-related by the
485 investigators. Among the 331 VELCADE treated patients, the most commonly reported
486 drug-related event leading to discontinuation was peripheral neuropathy (8%). Among
487 the 332 patients in the dexamethasone group, the most commonly reported drug-related
488 events leading to treatment discontinuation were psychotic disorder and hyperglycemia
489 (2% each).

490 Four deaths were considered to be VELCADE related in the phase 3 study: 1 case each of
491 cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest.
492 Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of
493 bacterial meningitis, and 1 case of sudden death at home.

494 The most common adverse events from the phase 3 study are shown in **Table 6**. All
495 adverse events with incidence $\geq 10\%$ in the VELCADE arm are included.

496

497
498

Table 6: Most Commonly Reported Adverse Events (≥10% in VELCADE arm), with Grades 3 and 4 Intensity in the Phase 3 Randomized Study (N=663)

Adverse Event	Treatment Group					
	VELCADE (n=331) [n (%)]			Dexamethasone (n=332) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events	All Events	Grade 3 Events	Grade 4 Events
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6(2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy ^a	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	35 (5)	5 (1)
Anorexia and appetite decreased	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Paresthesia and dysesthesia	91 (27)	6 (2)	0	38 (11)	1 (<1)	0
Anemia	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Headache	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Lower respiratory/lung infections	48 (15)	12 (4)	2 (<1)	69 (21)	36 (5)	3 (<1)
Pain in limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Back pain	46 (14)	10 (3)	0	33 (10)	4 (1)	0
Arthralgia	45 (14)	3 (<1)	0	35 (11)	5 (2)	0
Dizziness (excl. vertigo)	45 (14)	3 (<1)	0	34 (10)	0	0
Nasopharyngitis	45 (14)	1 (<1)	0	22 (7)	0	0
Herpes zoster	42 (13)	6 (2)	0	15 (5)	4 (1)	1 (<1)
Muscle cramps	41 (12)	0	0	50 (15)	3 (<1)	0
Myalgia	39 (12)	1 (<1)	0	18 (5)	1 (<1)	0
Rigors	37 (11)	0	0	8 (2)	0	0
Edema lower limb	35 (11)	0	0	43 (13)	1 (<1)	0

499

500 ^a Peripheral neuropathy includes all terms under peripheral neuropathy NEC, (peripheral neuropathy NOS,
501 peripheral neuropathy aggravated, peripheral sensory neuropathy, and peripheral motor neuropathy, and
502 neuropathy NOS).

503 **Non-randomized Phase 2 Clinical Studies**

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

508 The most commonly reported adverse events were asthenic conditions (including fatigue,
509 malaise, and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased
510 (including anorexia), constipation, and thrombocytopenia (each 43%), peripheral
511 neuropathy (including peripheral sensory neuropathy and peripheral neuropathy
512 aggravated) (37%), pyrexia and vomiting (each 36%), and anemia (32%). Fourteen
513 percent (14%) of patients experienced at least 1 episode of Grade 4 toxicity; the most
514 common toxicities were thrombocytopenia (3%) and neutropenia (3%).

515 **Serious Adverse Events (SAEs)**

516 A total of 113 (50%) of the 228 patients in the phase 2 studies experienced SAEs during
517 the studies. The most commonly reported SAEs included pyrexia and pneumonia (each
518 7%), diarrhea (6%), vomiting and dehydration (each 5%), and nausea (4%).

519 In the phase 2 clinical studies, adverse events thought by the investigator to be drug-
520 related and leading to discontinuation occurred in 18% of patients. The reasons for
521 discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), and
522 diarrhea and fatigue (each 2%).

523 Two deaths were reported and considered by the investigator to be possibly related to
524 study drug: 1 case of cardiopulmonary arrest and 1 case of respiratory failure.

525 The most common adverse events are shown in **Table 7**. All adverse events occurring at
526 $\geq 10\%$ are included. In the single-arm studies conducted, it is often not possible to
527 distinguish between adverse events that are drug-caused and those that reflect the
528 patient's underlying disease. Please see the discussion of specific adverse reactions that
529 follows.

530
531

Table 7: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events in the Phase 2 Studies using the 1.3 mg/m² dose (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

532

The Phase 2 Open-Label Extension Study

533 In the phase 2 extension study of 63 patients noted above (see **CLINICAL STUDIES**)
534 no new cumulative or new long term toxicities were observed with prolonged VELCADE
535 treatment.

536

Description of Selected Adverse Events from the Phase 3 and Phase 2 Studies

537

538 **Gastrointestinal Events**

539 In the phase 3 trial, 89% of patients on the VELCADE arm and 54% of patients on the
540 dexamethasone arm experienced at least one GI disorder. The most common GI
541 disorders in VELCADE patients included nausea, diarrhea, constipation, vomiting, and
542 anorexia. Grade 3 GI events occurred in 18% of patients on the VELCADE arm and 6%
543 of patients on the dexamethasone arm; Grade 4 events were rare (<1%) in both groups.
544 GI events were considered serious in 9% and 5% of the VELCADE and dexamethasone
545 patients, respectively. Six percent (6%) of patients on the VELCADE arm and 2% of
546 patients on the dexamethasone arm discontinued due to a GI event. The majority of
547 patients also experienced GI events during the phase 2 studies. These events were Grade
548 3 or 4 in 21% of patients and serious in 13% of patients.

549 **Thrombocytopenia**

550 In both the phase 3 and phase 2 studies, VELCADE associated thrombocytopenia was
551 characterized by a decrease in platelet count during the dosing period (days 1 to 11) and a
552 return toward baseline during the 10-day rest period during each treatment cycle. In the
553 phase 3 trial, thrombocytopenia was reported in 35% and 11% of patients on the
554 VELCADE and dexamethasone arms, respectively. On the VELCADE arm
555 thrombocytopenia was reported as Grade 3 in 26%, Grade 4 in 4%, and serious in 2% of
556 patients, and the event resulted in VELCADE discontinuation in 2% of patients. In the
557 phase 2 studies, thrombocytopenia was reported in 43% of patients, and 4% of those
558 patients discontinued VELCADE treatment due to thrombocytopenia (**see**
559 **PRECAUTIONS**).

560

561 **Peripheral Neuropathy**

562

563 In the phase 3 trial, peripheral neuropathy NEC occurred in 36% of patients on the
564 VELCADE arm and in 9% of patients on the dexamethasone arm. Peripheral neuropathy
565 was Grade 3 for 7% of patients and Grade 4 for <1% of patients on the VELCADE arm.
566 Eight percent (8%) of patients discontinued VELCADE due to peripheral neuropathy. Of
567 the 87 patients who experienced \geq Grade 2 peripheral neuropathy, 51% had improved or
568 resolved with a median of 3.5 months from first onset.

569 In the phase 2 studies, 81% of patients (173 of 214) starting at the 1.3 mg/m² dose and
570 with data available, had symptoms or signs of peripheral neuropathy at baseline
571 evaluation. In 62% of these patients (108 of 173), no new onset or worsening of
572 neuropathy was reported during treatment with VELCADE. New or worsening
573 peripheral neuropathy NEC among all patients in the phase 2 studies treated with the
574 1.3mg/m² dose was Grade 3 in 14% (31 of 228), and there were no Grade 4 events. Six
575 percent (6%) of patients (13 of 228) discontinued VELCADE due to peripheral
576 neuropathy. Among the patients with peripheral neuropathy that was Grade 2 and led to
577 discontinuation or was \geq Grade 3, 73% (24 of 33) reported improvement or resolution
578 following VELCADE dose adjustment, with a median time to improvement of one Grade
579 or more from the last dose of VELCADE of 33 days (**see PRECAUTIONS**).

580 **Hypotension**

581 In the phase 3 study, the incidence of hypotension (postural hypotension, orthostatic
582 hypotension and hypotension NOS) was 11% on the VELCADE arm compared to 2% on
583 the dexamethasone arm. Hypotension was Grade 1 or 2 in the majority of patients and
584 Grade 3 in <1%. Two percent (2%) of patients on the VELCADE arm had hypotension
585 reported as an SAE, and <1% discontinued due to hypotension. Similar incidences were
586 reported in the phase 2 studies. In addition, 4% of patients in phase 2 experienced
587 hypotension and had a concurrent syncopal event. Doses of antihypertensive medications
588 may need to be adjusted in patients receiving VELCADE.

589 **Neutropenia**

590 In the phase 3 study, neutrophil counts decreased during the VELCADE dosing period
591 (days 1 to 11) and returned toward baseline during the 10-day rest period during each
592 treatment cycle. Neutropenia occurred in 19% and 2% of patients in the VELCADE and
593 dexamethasone arms respectively. In the VELCADE arm, neutropenia was Grade 3 in
594 12% of patients and Grade 4 in 2%. No patient discontinued due to Grade 4 neutropenia.
595 In the phase 2 trials, neutropenia occurred in 24% of patients and was Grade 3 in 13%
596 and Grade 4 in 3%. The incidence of febrile neutropenia was <1% in both the phase 3
597 and phase 2 trials.

598 **Asthenic conditions (Fatigue, Malaise, Weakness)**

599 In the phase 3 trial, asthenia was reported in 61% and 45% of patients on the VELCADE
600 and dexamethasone arms respectively. Asthenia was \geq Grade 3 for 12% and 6% of
601 patients on the VELCADE and dexamethasone arms respectively. Three percent (3%) of
602 patients in the VELCADE group and 2% of patients in the dexamethasone group
603 discontinued treatment due to asthenia. Similar results were reported in the phase 2 trials.

604 **Pyrexia**

605 Pyrexia ($>38^{\circ}\text{C}$) was reported as an adverse event for 35% of patients on the VELCADE
606 arm and 16% of patients on the dexamethasone arm in the phase 3 trial. On the
607 VELCADE arm this event was Grade 3 in 2%; no Grade 4 pyrexia was reported. Similar
608 results were reported in the phase 2 trials.

609 **Additional Serious Adverse Events from Clinical Studies and Post-Marketing**

610
611 The following clinically important SAEs that are not described above have been reported
612 in clinical trials in patients treated with VELCADE administered as monotherapy or in
613 combination with other chemotherapeutics. These studies were conducted in patients
614 with hematological malignancies and in solid tumors.

615

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

617

618 **Cardiac disorders:** Angina pectoris, atrial fibrillation aggravated, atrial flutter,
619 bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block,
620 myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, Torsades
621 de pointes, ventricular tachycardia

622 **Ear and labyrinth disorders:** Hearing impaired, vertigo

623 **Eye disorders:** Diplopia

624 **Gastrointestinal disorders:** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis
625 hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal
626 obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large
627 intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae

628 **General disorders and administration site conditions:** Injection site erythema, neuralgia

629 **Hepatobiliary disorders:** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal
630 vein thrombosis, hepatitis

631 **Immune system disorders:** Anaphylactic reaction, drug hypersensitivity, immune
632 complex mediated hypersensitivity

633

634 **Infections and infestations:** Aspergillosis, bacteremia, urinary tract infection,, herpes
635 viral infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis

636

637 **Injury, poisoning and procedural complications:** Skeletal fracture, subdural hematoma
638

639 **Metabolism and nutrition disorders:** Hypocalcemia, hyperuricemia, hypokalemia,
640 hyperkalemia, hyponatremia, hypernatremia

641

642 **Nervous system disorders:** Ataxia, coma, dysarthria, dysautonomia, encephalopathy,
643 cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord
644 compression, paraplegia, transient ischemic attack

645

646 **Psychiatric disorders:** Agitation, confusion, mental status change, psychotic disorder,
647 suicidal ideation

648

649 **Renal and urinary disorders:** Calculus renal, bilateral hydronephrosis, bladder spasm,
650 hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure
651 (acute and chronic), glomerular nephritis proliferative

652

653 **Respiratory, thoracic and mediastinal disorders:** Acute respiratory distress syndrome,
654 aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated,

655 dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration,
656 pleural effusion, pneumonitis, respiratory distress

657 ***Skin and subcutaneous tissue disorders:*** Urticaria, face edema

658 ***Vascular disorders:*** Cerebrovascular accident, cerebral hemorrhage, deep venous
659 thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

660 **Post-Marketing Experience**

661 Clinically significant adverse events are listed here if they have been reported during
662 post-approval use of VELCADE and either they have not been reported in clinical trials,
663 or they have been reported in clinical trials, but their occurrence in the post-approval
664 setting is considered meaningful:

665 Atrioventricular block complete, cardiac tamponade, ischemic colitis,
666 encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular
667 coagulation, hepatitis and acute pancreatitis.

668 **OVERDOSAGE**

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

675

676 Overdosage more than twice the recommended dose has been associated with the acute
677 onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

678

679 There is no known specific antidote for VELCADE overdose. In the event of an
680 overdose, the patient's vital signs should be monitored and appropriate supportive care
681 given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and
682 body temperature (**see PRECAUTIONS and DOSAGE AND ADMINISTRATION**)

683 **DOSAGE AND ADMINISTRATION**

684 The recommended dose of VELCADE is 1.3 mg/m²/dose administered as a 3 to 5 second
685 bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a
686 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, VELCADE
687 may be administered on the standard schedule or on a maintenance schedule of once
688 weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to
689 35) (**see CLINICAL STUDIES section for a description of dose administration**
690 **during the trials**). At least 72 hours should elapse between consecutive doses of
691 VELCADE.

692

693 ***Dose Modification and Re-initiation of Therapy***

694
 695 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or
 696 Grade 4 hematological toxicities excluding neuropathy as discussed below (**see**
 697 **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE
 698 therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0
 699 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

700 **Table 8** contains the recommended dose modification for the management of patients
 701 who experience VELCADE related neuropathic pain and/or peripheral neuropathy.
 702 Patients with preexisting severe neuropathy should be treated with VELCADE only after
 703 careful risk-benefit assessment.

704 **Table 8: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or**
 705 **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 (disabling)	Discontinue VELCADE

706 Grading based on NCI Common Toxicity Criteria CTCAE v3.0 -

707
 708 **Administration Precautions:** VELCADE is an antineoplastic. Caution should be used
 709 during handling and preparation. Proper aseptic technique should be used. Use of gloves
 710 and other protective clothing to prevent skin contact is recommended. In clinical trials,
 711 local skin irritation was reported in 5% of patients, but extravasation of VELCADE was
 712 not associated with tissue damage.

713
 714 **Reconstitution/Preparation for Intravenous Administration:** Prior to use, the contents
 715 of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride
 716 Injection, USP. The reconstituted product should be a clear and colorless solution.

717
 718 Parenteral drug products should be inspected visually for particulate matter and
 719 discoloration prior to administration whenever solution and container permit. If any
 720 discoloration or particulate matter is observed, the reconstituted product should not be
 721 used.

722
 723 **Stability:** Unopened vials of VELCADE are stable until the date indicated on the package
 724 when stored in the original package protected from light.

725
 726 VELCADE contains no antimicrobial preservative. When reconstituted as directed,
 727 VELCADE may be stored at 25°C (77°F). Reconstituted VELCADE should be
 728 administered within 8 hours of preparation. The reconstituted material may be stored in

729 the original vial and/or the syringe prior to administration. The product may be stored for
730 up to 8 hours in a syringe; however total storage time for the reconstituted material must
731 not exceed 8 hours when exposed to normal indoor lighting.

732

733 **HOW SUPPLIED**

734

735 VELCADE[®] (bortezomib) for Injection is supplied as individually cartoned 10 mL vials
736 containing 3.5 mg of bortezomib as a white to off-white cake or powder.

737

738 NDC 63020-049-01

739 3.5 mg single dose vial

740

741 **STORAGE**

742

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

746

747 **Caution:** Rx only

748

749 U.S. Patents: 5,780,454; 6,083,903; 6,297,217; 6,617,317; 6,713, 446; 6,747,150 B2

750

751 ***Distributed and Marketed by:***

752 Millennium Pharmaceuticals, Inc.

753 40 Landsdowne Street.

754 Cambridge, MA 02139

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769

770 **VELCADE[®] (bortezomib) for Injection**

771

772 **PATIENT INFORMATION**

773

774 VELCADE is intended for use under the guidance and supervision of a healthcare
775 professional. Please discuss the possibility of the following side effects with your doctor:

776

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

778 VELCADE may cause low blood pressure that may lead to tiredness, dizziness, fainting,
779 or blurred vision. Do not drive any vehicle or operate any dangerous tools or machinery
780 if you experience these side effects. Even if you have not felt these effects previously,
781 you must still be cautious.

782

783 ***Pregnancy/Nursing:*** Please use effective contraceptive measures to prevent pregnancy
784 during treatment with VELCADE. It is advised that you are not given VELCADE if you
785 are pregnant. You must make sure that you do not become pregnant while receiving
786 VELCADE, but if you do, inform your doctor immediately. It is advised that you do not
787 breast feed while you are receiving VELCADE. If you wish to restart breast feeding after
788 your VELCADE treatment, you must discuss this with your doctor or nurse, who will tell
789 you when it is safe to do so.

790

791 ***Dehydration/Hypotension:*** Following the use of VELCADE therapy, you may
792 experience vomiting and/or diarrhea. Drink plenty of fluids. Speak with your doctor if
793 these symptoms occur about what you should do to control or manage these symptoms.
794 If you experience symptoms of dizziness or light-headedness, consult a healthcare
795 professional. Seek immediate medical attention if you experience fainting spells.

796

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

799 ***Diabetic Patients:*** If you are a patient on oral antidiabetic medication while receiving
800 VELCADE treatment, please check your blood sugar level frequently. Please call your
801 doctor if you notice an unusual change.

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

805 ***Congestive Heart Failure:*** Contact your doctor if you experience shortness of breath or
806 swelling of the feet, ankles, or legs.

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