

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

2 **PRESCRIBING INFORMATION**

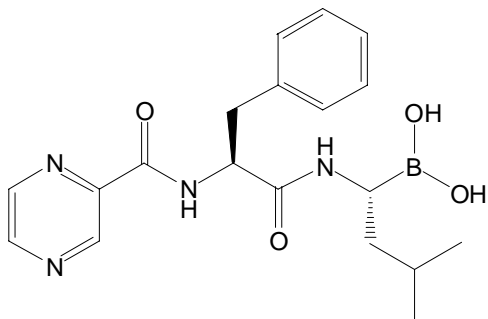
3 **DESCRIPTION**

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

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

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

13 Bortezomib has the following chemical structure:



15 The molecular weight is 384.24. The molecular formula is C₁₉H₂₅BN₄O₄. The solubility of
16 bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to
17 6.5.

18 **CLINICAL PHARMACOLOGY**

19 ***Mechanism of Action***

20 Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in
21 mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated
22 proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular
23 concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of
24 the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling
25 cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell
26 death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell
27 types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models,
28 including multiple myeloma.

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30 ***Pharmacokinetics***

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

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39 ***Distribution***

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

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44 ***Metabolism***

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

53 ***Elimination***

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

55 ***Special Populations***

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

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

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

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

64 ***Drug Interactions***

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

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

68 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and
69 3A4, with IC₅₀ values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC₅₀ =
70 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

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

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74 **CLINICAL STUDIES**

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

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

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

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

88 **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 $< 75 \times 10^9/L$	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%

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

96 Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles
97 followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone
98 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a
99 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone 40
100 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5
101 to 28). Patients with documented progressive disease on dexamethasone were offered
102 VELCADE at a standard dose and schedule on a companion study.

103 Following a preplanned interim analysis of time to progression, the dexamethasone arm was
104 halted and all patients randomized to dexamethasone were offered VELCADE, regardless of
105 disease status. At this time of study termination, a final statistical analysis was performed. Due

106 to this early termination of the study, the median duration of follow-up for surviving patients
107 (n=534) is limited to 8.3 months.

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

113 The time to event analyses and response rates from the phase 3 trial are presented in **Table 2**.
114 Response and progression were assessed using the European Group for Blood and Marrow
115 Transplantation (EBMT) criteria.¹ Complete response (CR) required < 5% plasma cells in the
116 marrow, 100% reduction in M-protein, and a negative immunofixation test (IF⁻). Partial
117 Response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine
118 myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable
119 bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the
120 criteria for complete response including 100% reduction in M-protein by protein electrophoresis,
121 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

Efficacy Endpoint	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
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.

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

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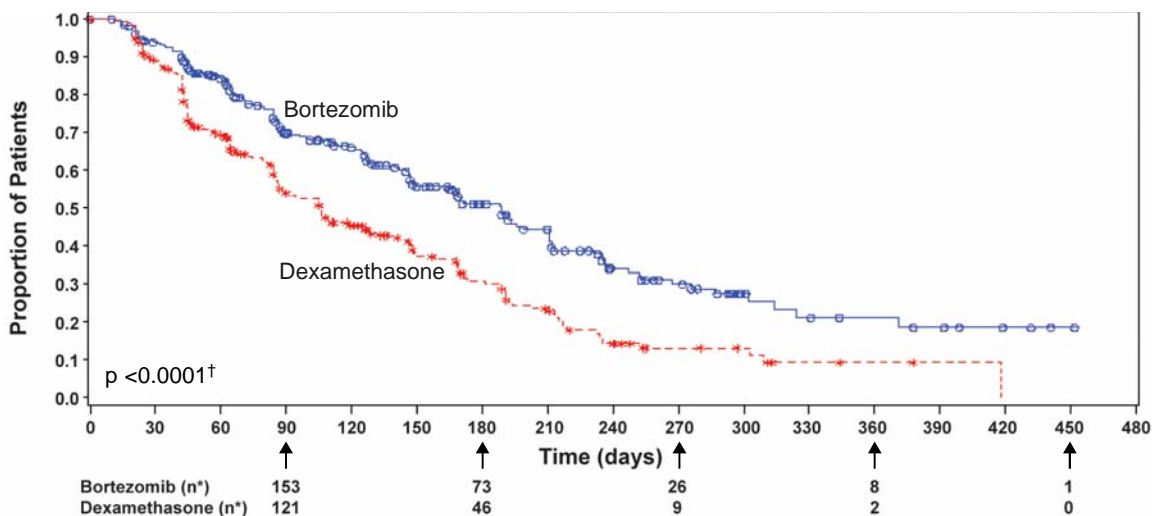
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**Fig. 1: Time to Progression
 Bortezomib vs. Dexamethasone**



* Patients remaining after the indicated timepoint
 † p-value from log-rank test

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

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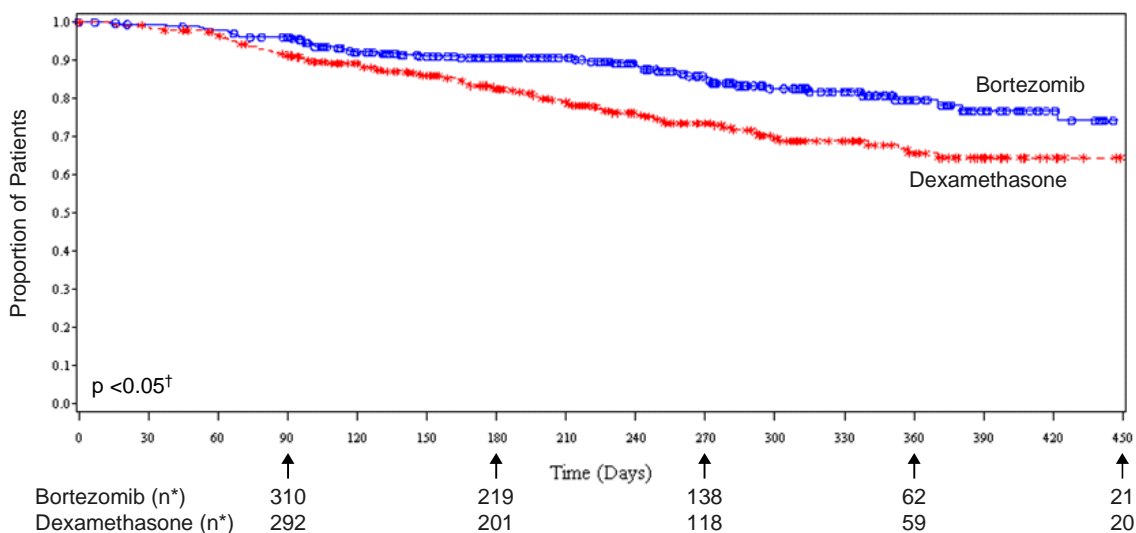
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**Fig. 2: Overall Survival
 Bortezomib vs. Dexamethasone**



* Patients remaining after the indicated timepoint
 † p-value from log-rank test

180 For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median
 181 duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI:

182 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was
183 significantly higher on the VELCADE arm regardless of β_2 -microglobulin levels at
184 baseline.

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

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

192 An IV bolus injection of VELCADE 1.3 mg/m²/dose was administered twice weekly for
193 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a
194 maximum of 8 treatment cycles. The study employed dose modifications for toxicity (**see**
195 **DOSAGE AND ADMINISTRATION**). Patients who experienced a response to
196 VELCADE were allowed to continue VELCADE treatment in an extension study.

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

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 β_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%

199 * Based on number of patients with baseline data available

200 Responses to VELCADE alone are shown in **Table 4**. Response rates to VELCADE
201 alone were determined by an independent review committee (IRC) based on EBMT
202 criteria.¹ Response rates using the Southwest Oncology Group (SWOG) criteria² are also
203 shown. SWOG response required a $\geq 75\%$ reduction in serum myeloma protein and/or
204 $\geq 90\%$ urine protein. A total of 188 patients were evaluable for response; 9 patients with
205 nonmeasurable disease could not be evaluated for response by the IRC, and 5 patients
206 were excluded from the efficacy analyses because they had had minimal prior therapy.
207 The mean number of cycles administered was 6. The median time to response was 38
208 days (range 30 to 127 days). The median survival of all patients enrolled was 17 months
209 (range <1 to 36+ months).

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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)

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

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

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

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

224 An open-label, multicenter study randomized 54 patients with multiple myeloma who had
225 progressed or relapsed on or after front-line therapy to receive VELCADE 1.0 mg/m² or
226 1.3 mg/m² IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-
227 day rest period (Days 12 to 21). The median duration of time between diagnosis of
228 multiple myeloma and first dose of VELCADE on this trial was 2.0 years, and patients
229 had received a median of 1 prior line of treatment (median of 3 prior therapies). A single
230 complete response was seen at each dose. The overall response rates (CR + PR) were
231 30% (8/27) at 1.0 mg/m² and 38% (10/26) at 1.3 mg/m².

232 *A Phase 2 Open-Label Extension Study*

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

244 **INDICATIONS AND USAGE**

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

247 **CONTRAINDICATIONS**

248 VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or
249 mannitol.

250 **WARNINGS**

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

253 ***Pregnancy Category D***

254 Women of childbearing potential should avoid becoming pregnant while being treated
255 with VELCADE.
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257 Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and
258 rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m² in the rat and 0.05 mg/kg; 0.6
259 mg/m² in the rabbit) when administered during organogenesis. These dosages are
260 approximately half the clinical dose of 1.3 mg/m² based on body surface area.
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262 Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6
263 mg/m²) experienced significant post-implantation loss and decreased number of live
264 fetuses. Live fetuses from these litters also showed significant decreases in fetal weight.
265 The dose is approximately 0.5 times the clinical dose of 1.3 mg/m² based on body surface
266 area.

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

271 **PRECAUTIONS**

272 ***Peripheral Neuropathy:*** VELCADE treatment causes a peripheral neuropathy that is
273 predominantly sensory. However, cases of severe sensory and motor peripheral
274 neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or
275 a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may
276 experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with
277 VELCADE. Patients should be monitored for symptoms of neuropathy, such as a
278 burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort or neuropathic
279 pain. Patients experiencing new or worsening peripheral neuropathy may require change
280 in the dose and schedule of VELCADE (**see DOSAGE AND ADMINISTRATION**).
281 Following dose adjustments, improvement in or resolution of peripheral neuropathy was
282 reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the phase 3 study.
283 Improvement in or resolution of peripheral neuropathy was reported in 73% of patients
284 who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral
285 neuropathy in the phase 2 studies (**also see ADVERSE REACTIONS**).

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

293 **Cardiac Disorders:** Acute development or exacerbation of congestive heart failure,
294 and/or new onset of decreased left ventricular ejection fraction has been reported,
295 including reports in patients with few or no risk factors for decreased left ventricular
296 ejection fraction. Patients with risk factors for, or existing heart disease should be closely
297 monitored. In the phase 3 study, the incidence of any treatment-emergent cardiac
298 disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively.
299 The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive
300 cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and
301 dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-
302 interval prolongation in clinical studies; causality has not been established.

303 **Pulmonary Disorders:** There have been rare reports of acute diffuse infiltrative
304 pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung
305 infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving
306 VELCADE. Some of these events have been fatal. A higher proportion of these events
307 have been reported in Japan. In the event of new or worsening pulmonary symptoms, a
308 prompt diagnostic evaluation should be performed and patients treated appropriately.
309

310 In a clinical trial, the first two patients given high-dose cytarabine (2g/m² per day) by
311 continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous
312 leukemia died of ARDS early in the course of therapy.

313 **Laboratory Tests:** Complete blood counts (CBC) should be frequently monitored
314 throughout treatment with VELCADE.

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

319 **Thrombocytopenia/Neutropenia:** VELCADE is associated with thrombocytopenia and
320 neutropenia (see **ADVERSE EVENTS**). Platelets and neutrophils were lowest at Day 11
321 of each cycle of VELCADE treatment and typically recovered to baseline by the next
322 cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained
323 consistent over the 8 cycles of twice weekly dosing, and there was no evidence of
324 cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured
325 was approximately 40% of baseline. The severity of thrombocytopenia related to
326 pretreatment platelet count is shown in **Table 5** for the phase 3 study. In the phase 3
327 study, the incidence of significant bleeding events (\geq Grade 3) was similar on both the
328 VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored

329 prior to each dose of VELCADE. VELCADE therapy should be held when the platelet
330 count is <25,000/ μ L and reinitiated at a reduced dose (see **DOSAGE AND**
331 **ADMINISTRATION and ADVERSE REACTIONS**). There have been reports of
332 gastrointestinal and intracerebral hemorrhage in association with VELCADE.
333 Transfusions may be considered. The incidence of febrile neutropenia was <1% in both
334 the phase 3 and phase 2 trials.

335 **Table 5: Severity of Thrombocytopenia Related to**
336 **Pretreatment Platelet Count in the 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
$\geq 75,000/\mu\text{L}$	309	8 (3%)	36 (12%)
$\geq 50,000/\mu\text{L}$ - <75,000/ μL	14	2 (14%)	11 (79%)
$\geq 10,000/\mu\text{L}$ -<50,000/ μL	7	1 (14%)	5 (71%)

337 * A baseline platelet count of 50,000/ μ L was required for study eligibility.

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

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

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

344 **Hepatic Events**

345 Rare cases of acute liver failure have been reported in patients receiving multiple
346 concomitant medications and with serious underlying medical conditions. Other reported
347 hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis.
348 Such changes may be reversible upon discontinuation of VELCADE. There is limited re-
349 challenge information in these patients.

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

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

359 **Animal Toxicity Findings**

360 *Cardiovascular toxicity*

361 Studies in monkeys showed that administration of dosages approximately twice the
362 recommended clinical dose resulted in heart rate elevations, followed by profound
363 progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses

364 ≥ 1.2 mg/m² induced dose-proportional changes in cardiac parameters. Bortezomib has
365 been shown to distribute to most tissues in the body, including the myocardium. In a
366 repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and
367 necrosis were also observed.

368

369 *Chronic Administration*

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

377 *Information for Patients*

378 Physicians are advised to discuss the PATIENT INFORMATION section with patients
379 prior to treatment with VELCADE (see PATIENT INFORMATION).

380

381 *Ability to Drive or Operate Machinery or Impairment of Mental Ability:* VELCADE may
382 cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Patients should be
383 advised not to drive or operate machinery if they experience these symptoms.

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

388 *Drug Interactions*

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

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

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

399 *Drug Laboratory Test Interactions*

400 None known.

401 *Carcinogenesis, Mutagenesis, Impairment of Fertility*

402 Carcinogenicity studies have not been conducted with bortezomib.

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

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

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

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

415 ***Nursing Mothers***

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

420 ***Pediatric Use***

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

422 ***Geriatric Use***

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

431 In the phase 2 clinical study of 202 patients, 35% of patients were 65 years of age or
432 older, the incidence of Grade ≥ 3 events was 74%, 80%, and 85% for VELCADE patients
433 ≤ 50 , 51 to 65, and >65 years old, respectively (see **CLINICAL STUDIES**).

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

437

438 **ADVERSE REACTIONS**

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

440 Among the 331 VELCADE treated patients, the most commonly reported events overall
441 were asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%),
442 peripheral neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric
443 disorders (each 35%), anorexia and appetite decreased (34%), paresthesia and dysesthesia
444 (27%), anemia and headache (each 26%), and cough (21%). The most commonly

445 reported adverse events reported among the 332 patients in the dexamethasone group
446 were psychiatric disorders (49%), asthenic conditions (45%), insomnia (27%), anemia
447 (22%), and diarrhea and lower respiratory/lung infections (each 21%). Fourteen percent
448 (14%) of patients in the VELCADE treated arm experienced a Grade 4 adverse event; the
449 most common toxicities were thrombocytopenia (4%), neutropenia (2%) and
450 hypercalcemia (2%). Sixteen percent (16%) of dexamethasone treated patients
451 experienced a Grade 4 adverse event; the most common toxicity was hyperglycemia
452 (2%).

453 ***Serious Adverse Events (SAEs)***

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

462 A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment
463 group and 61 (18%) of 332 patients in the dexamethasone treatment group were
464 discontinued from treatment due to adverse events assessed as drug-related by the
465 investigators. Among the 331 VELCADE treated patients, the most commonly reported
466 drug-related event leading to discontinuation was peripheral neuropathy (8%). Among
467 the 332 patients in the dexamethasone group, the most commonly reported drug-related
468 events leading to treatment discontinuation were psychotic disorder and hyperglycemia
469 (2% each).

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

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

476
477

**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
	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)	26 (8)	3 (<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)	24 (7)	1 (<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

478
479
480

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

481 *Non-randomized Phase 2 Clinical Studies*

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

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

493 *Serious Adverse Events (SAEs)*

494 A total of 113 (50%) of the 228 patients in the phase 2 studies experienced SAEs during
495 the studies. The most commonly reported SAEs included pyrexia and pneumonia (each
496 7%), diarrhea (6%), vomiting and dehydration (each 5%), and nausea (4%).

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

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

503 The most common adverse events are shown in **Table 7**. All adverse events occurring at
504 $\geq 10\%$ are included. In the single-arm studies conducted, it is often not possible to
505 distinguish between adverse events that are drug-caused and those that reflect the
506 patient's underlying disease. Please see the discussion of specific adverse reactions that
507 follows.

508 **Table 7: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events in the Phase 2**
509 **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

510

511 ***The Phase 2 Open-Label Extension Study***

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

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

516 ***Gastrointestinal Events***

517 In the phase 3 trial, 89% of patients on the VELCADE arm and 54% of patients on the
518 dexamethasone arm experienced at least one GI disorder. The most common GI
519 disorders in VELCADE patients included nausea, diarrhea, constipation, vomiting, and
520 anorexia. Grade 3 GI events occurred in 18% of patients on the VELCADE arm and 6%
521 of patients on the dexamethasone arm; Grade 4 events were rare (<1%) in both groups.
522 GI events were considered serious in 9% and 5% of the VELCADE and dexamethasone
523 patients, respectively. Six percent (6%) of patients on the VELCADE arm and 2% of
524 patients on the dexamethasone arm discontinued due to a GI event. The majority of
525 patients also experienced GI events during the phase 2 studies. These events were Grade
526 3 or 4 in 21% of patients and serious in 13% of patients.

527 ***Thrombocytopenia***

528 In both the phase 3 and phase 2 studies, VELCADE associated thrombocytopenia was
529 characterized by a decrease in platelet count during the dosing period (days 1 to 11) and a
530 return toward baseline during the 10-day rest period during each treatment cycle. In the
531 phase 3 trial, thrombocytopenia was reported in 35% and 11% of patients on the
532 VELCADE and dexamethasone arms, respectively. On the VELCADE arm
533 thrombocytopenia was reported as Grade 3 in 26%, Grade 4 in 4%, and serious in 2% of
534 patients, and the event resulted in VELCADE discontinuation in 2% of patients. In the
535 phase 2 studies, thrombocytopenia was reported in 43% of patients, and 4% of those
536 patients discontinued VELCADE treatment due to thrombocytopenia (see
537 **PRECAUTIONS**).

538 ***Peripheral Neuropathy***

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

545 In the phase 2 studies, 81% of patients (173 of 214) starting at the 1.3 mg/m² dose and
546 with data available, had symptoms or signs of peripheral neuropathy at baseline
547 evaluation. In 62% of these patients (108 of 173), no new onset or worsening of
548 neuropathy was reported during treatment with VELCADE. New or worsening
549 peripheral neuropathy NEC among all patients in the phase 2 studies treated with the
550 1.3mg/m² dose was Grade 3 in 14% (31 of 228), and there were no Grade 4 events. Six
551 percent (6%) of patients (13 of 228) discontinued VELCADE due to peripheral
552 neuropathy. Among the patients with peripheral neuropathy that was Grade 2 and led to
553 discontinuation or was \geq Grade 3, 73% (24 of 33) reported improvement or resolution
554 following VELCADE dose adjustment, with a median time to improvement of one Grade
555 or more from the last dose of VELCADE of 33 days (see **PRECAUTIONS**).

556 ***Hypotension***

557 In the phase 3 study, the incidence of hypotension (postural hypotension, orthostatic
558 hypotension and hypotension NOS) was 11% on the VELCADE arm compared to 2% on

559 the dexamethasone arm. Hypotension was Grade 1 or 2 in the majority of patients and
560 Grade 3 in <1%. Two percent (2%) of patients on the VELCADE arm had hypotension
561 reported as an SAE, and <1% discontinued due to hypotension. Similar incidences were
562 reported in the phase 2 studies. In addition, 4% of patients in phase 2 experienced
563 hypotension and had a concurrent syncopal event. Doses of antihypertensive medications
564 may need to be adjusted in patients receiving VELCADE.

565 ***Neutropenia***

566 In the phase 3 study, neutrophil counts decreased during the VELCADE dosing period
567 (days 1 to 11) and returned toward baseline during the 10-day rest period during each
568 treatment cycle. Neutropenia occurred in 19% and 2% of patients in the VELCADE and
569 dexamethasone arms respectively. In the VELCADE arm, neutropenia was Grade 3 in
570 12% of patients and Grade 4 in 2%. No patient discontinued due to Grade 4 neutropenia.
571 In the phase 2 trials, neutropenia occurred in 24% of patients and was Grade 3 in 13%
572 and Grade 4 in 3%. The incidence of febrile neutropenia was <1% in both the phase 3
573 and phase 2 trials.

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

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

580 ***Pyrexia***

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

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

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

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

591 ***Cardiac disorders:*** Angina pectoris, atrial fibrillation aggravated, atrial flutter,
592 bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block,
593 myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, Torsades
594 de pointes, ventricular tachycardia

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

596 ***Eye disorders:*** Diplopia, conjunctival infection, irritation

- 597 ***Gastrointestinal disorders:*** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis
598 hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal
599 obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large
600 intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae,
601 gastroesophageal reflux
- 602 ***General disorders and administration site conditions:*** Injection site erythema, neuralgia
- 603 ***Hepatobiliary disorders:*** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal
604 vein thrombosis, hepatitis, liver failure
- 605 ***Immune system disorders:*** Anaphylactic reaction, drug hypersensitivity, immune
606 complex mediated hypersensitivity, angioedema, laryngeal edema
- 607 ***Infections and infestations:*** Aspergillosis, bacteremia, urinary tract infection, herpes
608 viral infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter
609 related infection
- 610 ***Injury, poisoning and procedural complications:*** Catheter related complication, skeletal
611 fracture, subdural hematoma
- 612 ***Metabolism and nutrition disorders:*** Hypocalcemia, hyperuricemia, hypokalemia,
613 hyperkalemia, hyponatremia, hypernatremia
- 614 ***Nervous system disorders:*** Ataxia, coma, dysarthria, dysautonomia, encephalopathy,
615 cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord
616 compression, paralysis, postherpetic neuralgia, transient ischemic attack
- 617 ***Psychiatric disorders:*** Agitation, confusion, mental status change, psychotic disorder,
618 suicidal ideation
- 619 ***Renal and urinary disorders:*** Calculus renal, bilateral hydronephrosis, bladder spasm,
620 hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure
621 (acute and chronic), glomerular nephritis proliferative
- 622 ***Respiratory, thoracic and mediastinal disorders:*** Acute respiratory distress syndrome,
623 aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated,
624 dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration,
625 pleural effusion, pneumonitis, respiratory distress
- 626 ***Skin and subcutaneous tissue disorders:*** Urticaria, face edema, rash, leukocytoclastic
627 vasculitis
- 628 ***Vascular disorders:*** Cerebrovascular accident, cerebral hemorrhage, deep venous
629 thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

630 **Post-Marketing Experience**

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

635 Atrioventricular block complete, cardiac tamponade, ischemic colitis,
636 encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular
637 coagulation, hepatitis, acute pancreatitis, acute diffuse infiltrative pulmonary disease
638 and toxic epidermal necrolysis.

639 **OVERDOSAGE**

640 In humans, overdosage more than twice the recommended dose has been associated with
641 the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

642 In monkeys and dogs, cardiovascular safety pharmacology studies show that IV doses
643 approximately 2 to 3 times the recommended clinical dose (on a mg/m^2 basis) are
644 associated with increases in heart rate, decreases in contractility, hypotension, and death.
645 The decreased cardiac contractility and hypotension responded to acute intervention with
646 positive inotropic or pressor agents. In dog studies, a slight increase in the corrected QT
647 interval was observed at a lethal dose.

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

652 **DOSAGE AND ADMINISTRATION**

653 The recommended dose of VELCADE is $1.3 \text{ mg}/\text{m}^2/\text{dose}$ administered as a 3 to 5 second
654 bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a
655 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, VELCADE
656 may be administered on the standard schedule or on a maintenance schedule of once
657 weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to
658 35) (see **CLINICAL STUDIES section for a description of dose administration**
659 **during the trials**). At least 72 hours should elapse between consecutive doses of
660 VELCADE.

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

662 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or
663 Grade 4 hematological toxicities excluding neuropathy as discussed below (see
664 **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE
665 therapy may be reinitiated at a 25% reduced dose ($1.3 \text{ mg}/\text{m}^2/\text{dose}$ reduced to 1.0
666 $\text{mg}/\text{m}^2/\text{dose}$; $1.0 \text{ mg}/\text{m}^2/\text{dose}$ reduced to $0.7 \text{ mg}/\text{m}^2/\text{dose}$).

667 **Table 8** contains the recommended dose modification for the management of patients
668 who experience VELCADE related neuropathic pain and/or peripheral neuropathy.

669 Patients with preexisting severe neuropathy should be treated with VELCADE only after
670 careful risk-benefit assessment.

671 **Table 8: Recommended Dose Modification for VELCADE related Neuropathic**
672 **Pain 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 reinstate 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

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

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

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

682 Parenteral drug products should be inspected visually for particulate matter and
683 discoloration prior to administration whenever solution and container permit. If any
684 discoloration or particulate matter is observed, the reconstituted product should not be
685 used.

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

688 VELCADE contains no antimicrobial preservative. When reconstituted as directed,
689 VELCADE may be stored at 25°C (77°F). Reconstituted VELCADE should be
690 administered within 8 hours of preparation. The reconstituted material may be stored in
691 the original vial and/or the syringe prior to administration. The product may be stored for
692 up to 8 hours in a syringe; however total storage time for the reconstituted material must
693 not exceed 8 hours when exposed to normal indoor lighting.
694

695 **HOW SUPPLIED**

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

698 NDC 63020-049-01
699 3.5 mg single dose vial

700 **STORAGE**

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

704

705 **Caution: R_x only**

706

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

708

709 ***Distributed and Marketed by:***

710 Millennium Pharmaceuticals, Inc.

711 40 Landsdowne Street

712 Cambridge, MA 02139

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714  **MILLENNIUM**[®]

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729 **VELCADE® (bortezomib) for Injection**
730 **PATIENT INFORMATION**

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

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

734 VELCADE may cause tiredness, dizziness, fainting, or blurred vision. Do not drive any
735 vehicle or operate any dangerous tools or machinery if you experience these side effects.
736 Even if you have not felt these effects previously, you must still be cautious.

737 ***Pregnancy/Nursing:***

738 Please use effective contraceptive measures to prevent pregnancy during treatment with
739 VELCADE. It is advised that you are not given VELCADE if you are pregnant. You
740 must make sure that you do not become pregnant while receiving VELCADE, but if you
741 do, inform your doctor immediately. It is advised that you do not breast feed while you
742 are receiving VELCADE. If you wish to restart breast feeding after your VELCADE
743 treatment, you must discuss this with your doctor or nurse, who will tell you when it is
744 safe to do so.

745 ***Dehydration/Hypotension:***

746 Following the use of VELCADE therapy, you may experience vomiting and/or diarrhea.
747 Drink plenty of fluids. Speak with your doctor if these symptoms occur about what you
748 should do to control or manage these symptoms. If you experience symptoms of
749 dizziness or light-headedness, consult a healthcare professional. Seek immediate medical
750 attention if you experience fainting spells.

751 ***Concomitant Medications:***

752 Please speak with your doctor about any other medication you are currently taking. Your
753 doctor will want to be aware of any other medications.

754 ***Diabetic Patients:***

755 If you are a patient on oral antidiabetic medication while receiving VELCADE treatment,
756 please check your blood sugar level frequently. Please call your doctor if you notice an
757 unusual change.

758 ***Peripheral Neuropathy:***

759 Contact your doctor if you experience new or worsening symptoms of peripheral
760 neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or
761 weakness in your arms or legs.

762 ***Congestive Heart Failure:***

763 Contact your doctor if you experience shortness of breath or swelling of the feet, ankles,
764 or legs.

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Rev 5