

1 **VELCADE<sup>®</sup> (bortezomib) for Injection**

2 **PRESCRIBING INFORMATION**

3 **DESCRIPTION**

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5 VELCADE<sup>®</sup> (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.

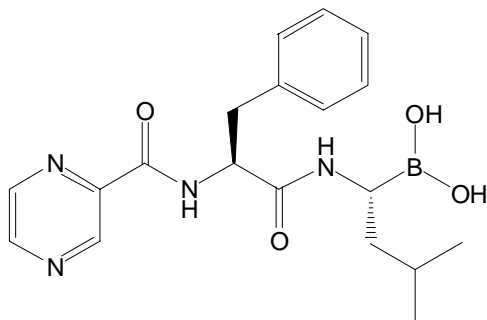
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14 The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-  
15 oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

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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 C<sub>19</sub>H<sub>25</sub>BN<sub>4</sub>O<sub>4</sub>. 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/m<sup>2</sup> 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/m<sup>2</sup> 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***

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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***

62

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**).

72

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**).

76

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 IC<sub>50</sub> values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC<sub>50</sub> =  
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 β<sub>2</sub>-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**

<b>Patient Characteristics</b>	<b>VELCADE N=333</b>	<b>Dexamethasone N=336</b>
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 $\leq 70$	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10 <sup>9</sup> /L	6%	4%
<b>Disease Characteristics</b>		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median $\beta_2$ -microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance $\leq 30$ mL/min [n (%)]	17 (5%)	11 (3%)
<b>Median Duration of Multiple Myeloma Since Diagnosis (Years)</b>		
	3.5	3.1
<b>Number of Prior Therapeutic Lines of Treatment</b>		
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%

105

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/m<sup>2</sup>/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/m<sup>2</sup>/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.<sup>1</sup> Complete response (CR) required < 5% plasma cells in the  
133 marrow, 100% reduction in M-protein, and a negative immunofixation test (IF<sup>-</sup>). 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<sup>+</sup>).

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

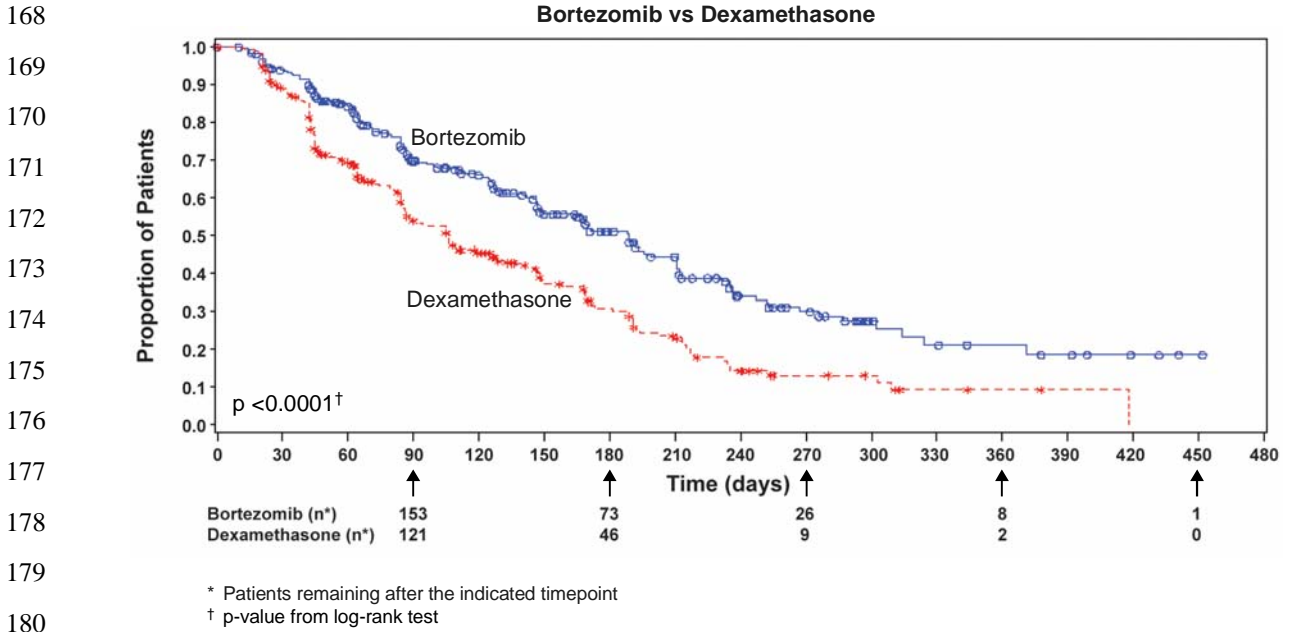
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<sup>a</sup> Kaplan-Meier estimate.  
<sup>b</sup> Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for VELCADE.  
<sup>c</sup> p-value based on the stratified log-rank test including randomization stratification factors.  
<sup>d</sup> Precise p-value cannot be rendered  
<sup>e</sup> Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.  
<sup>f</sup> EBMT criteria<sup>1</sup>; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria. nCR is in the PR category.  
<sup>g</sup> In 2 patients the IF was unknown.  
<sup>h</sup> p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors;  
<sup>i</sup> Not Estimable.  
<sup>j</sup> 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

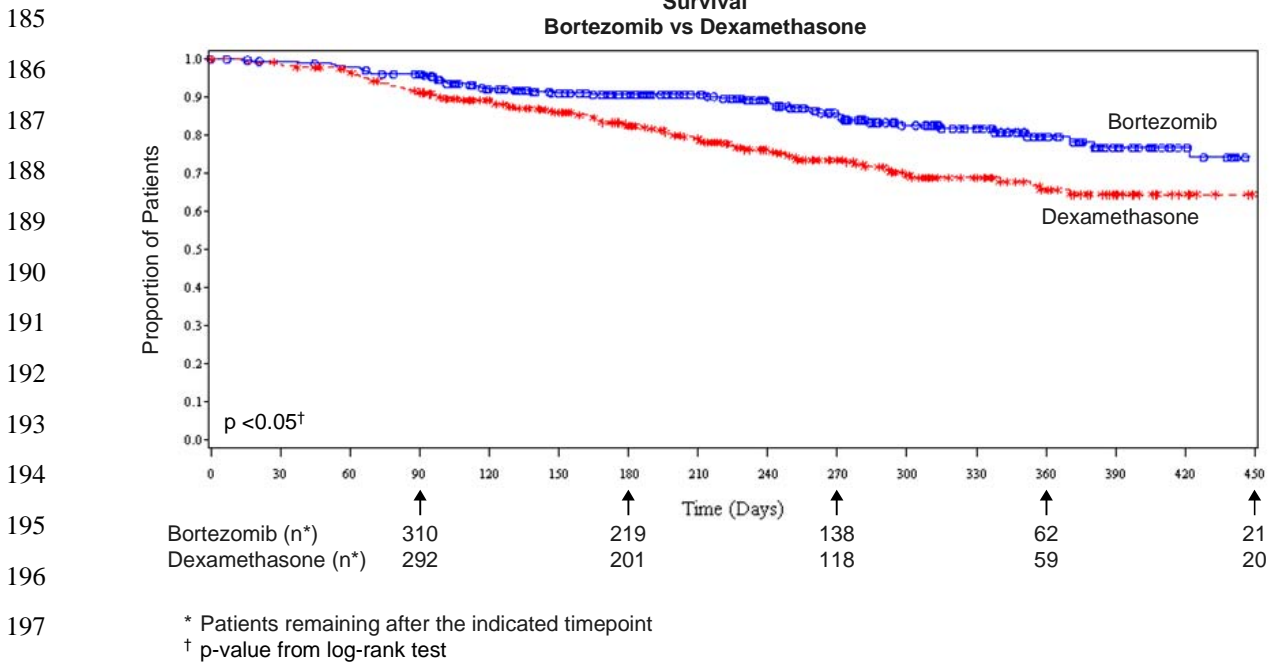
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181 As shown in Figure 2, VELCADE had a significant survival advantage relative to  
182 dexamethasone ( $p < 0.05$ ). The median follow-up was 8.3 months.

183

184 Figure 2: Overall Survival



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  $\beta_2$ -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/m<sup>2</sup>/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

	<b>N = 202</b>
<b>Patient Characteristics</b>	
Median age in years (range)	59 (34, 84)
Gender: male/female	60% / 40%
Race: Caucasian/Black/Other	81% / 10% / 8%
Karnofsky Performance Status score $\leq 70$	20%
Hemoglobin $< 100$ g/L	44%
Platelet count $< 75 \times 10^9$ /L	21%
<b>Disease Characteristics</b>	
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%
<b>Median Duration of Multiple Myeloma Since Diagnosis in Years</b>	<b>4.0</b>
<b>Previous Therapy</b>	
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.<sup>1</sup> Response rates using the Southwest Oncology Group (SWOG) criteria<sup>2</sup> 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)**

<b>Response Analyses (VELCADE monotherapy)</b>	<b>N = 188</b>	<b>N (%)</b>	<b>(95% CI)</b>
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) <sup>a</sup>		33 (18%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)		385 Days	(245, 538)

233 <sup>a</sup> **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.<sup>2</sup>

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/m<sup>2</sup> or  
 246 1.3 mg/m<sup>2</sup> 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/m<sup>2</sup> and 38% (10/26) at 1.3 mg/m<sup>2</sup>.

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<sup>®</sup> (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***

275

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/m<sup>2</sup> in the rat and 0.05 mg/kg; 0.6  
281 mg/m<sup>2</sup> in the rabbit) when administered during organogenesis. These dosages are  
282 approximately half the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

283

284 Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6  
285 mg/m<sup>2</sup>) 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/m<sup>2</sup> 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.

327  
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**

<b>Pretreatment Platelet Count*</b>	<b>Number of Patients (N=331)**</b>	<b>Number (%) of Patients with Platelet Count &lt;10,000/<math>\mu</math>L</b>	<b>Number (%) of Patients with Platelet Count 10,000-25,000/<math>\mu</math>L</b>
$\geq 75,000/\mu\text{L}$	309	8 (3%)	36 (12%)
$\geq 50,000/\mu\text{L}$ - $<75,000/\mu\text{L}$	14	2 (14%)	11 (79%)
$\geq 10,000/\mu\text{L}$ - $<50,000/\mu\text{L}$	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  $\text{mg/m}^2$ . 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  $\geq 65$  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  $\geq 65$  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  $\leq 50$ , 51-64 and  $\geq 65$  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  $\geq 3$  events was 74%, 80%, and 85% for VELCADE patients  
452  $\leq 50$ , 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
<b>Adverse Event</b>	<b>331 (100)</b>	<b>203 (61)</b>	<b>45 (14)</b>	<b>327 (98)</b>	<b>146 (44)</b>	<b>52 (16)</b>
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 <sup>a</sup>	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 <sup>a</sup> 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/m<sup>2</sup>/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 ≥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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup>/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/m<sup>2</sup>/dose reduced to 1.0  
 699 mg/m<sup>2</sup>/dose; 1.0 mg/m<sup>2</sup>/dose reduced to 0.7 mg/m<sup>2</sup>/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 <sup>2</sup>
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 <sup>2</sup> 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<sup>®</sup> (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

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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.

807

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815 Issued March 2005

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