

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

2 **PRESCRIBING INFORMATION**

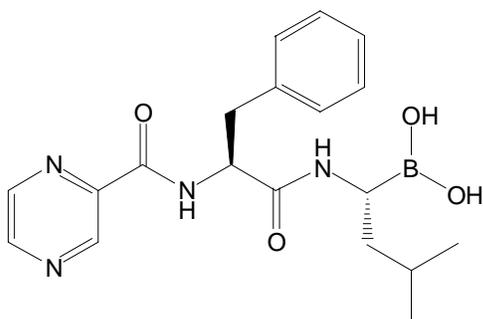
3 **DESCRIPTION**

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:



14

15 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  
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.

29 ***Pharmacokinetics***

30 Following intravenous administration of 1.0 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> doses to 24 patients with  
31 multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of  
32 bortezomib (C<sub>max</sub>) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In

33 subsequent doses, when administered twice weekly, the mean maximum observed plasma  
34 concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m<sup>2</sup> dose and 89 to 120 ng/mL for the  
35 1.3 mg/m<sup>2</sup> dose. The mean elimination half-life of bortezomib upon multiple dosing ranged  
36 from 40 to 193 hours after the 1.0 mg<sup>2</sup> dose and 76 to 108 hours after the 1.3mg/m<sup>2</sup> dose. The  
37 mean total body clearances was 102 and 112 L/h following the first dose for doses of 1.0 mg/m<sup>2</sup>  
38 and 1.3 mg/m<sup>2</sup>, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses  
39 of 1.0 and 1.3 mg/m<sup>2</sup>, respectively.

#### 40 ***Distribution***

41 The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m<sup>2</sup>  
42 following single- or repeat-dose administration of 1.0mg/m<sup>2</sup> or 1.3mg/m<sup>2</sup> to patients with  
43 multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The  
44 binding of bortezomib to human plasma proteins averaged 83% over the concentration range of  
45 100 to 1000 ng/mL.

#### 46 ***Metabolism***

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

#### 55 ***Elimination***

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

#### 57 ***Special Populations***

58 ***Age:*** Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients  
59 who had received intravenous doses of 1.0 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> showed that both dose-  
60 normalized AUC and C<sub>max</sub> tend to be less in younger patients. Patients < 65 years of age (n=26)  
61 had about 25% lower mean dose-normalized AUC and C<sub>max</sub> than those ≥ 65 years of age (n=13).

62 ***Gender:*** Mean dose-normalized AUC and C<sub>max</sub> values were comparable between male (n=22)  
63 and female (n=17) patients after the first dose of Cycle 1 for the 1.0 and 1.3 mg/m<sup>2</sup> doses

64 ***Race:*** The effect of race on exposure to bortezomib could not be assessed as most of the patients  
65 were Caucasian.

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

68 ***Renal Impairment:*** Clinical studies included patients with creatinine clearance values as low as  
69 13.8 mL/min (see **PRECAUTIONS**).

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

#### 71 ***Drug Interactions***

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

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

75 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and  
76 3A4, with IC<sub>50</sub> values of >30μM (>11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC<sub>50</sub> =  
77 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

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

#### 80 ***Pharmacodynamics***

81 Following twice weekly administration of 1.0 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> bortezomib doses (n=12 per  
82 each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in  
83 whole blood was observed 5 minutes after drug administration. Comparable maximum inhibition  
84 of 20S proteasome activity was observed between 1.0 and 1.3 mg/m<sup>2</sup> doses. Maximal inhibition  
85 ranged from 70% to 84% and from 73% to 83% for the 1.0 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> dose regimens,  
86 respectively.

#### 87 **CLINICAL STUDIES**

##### 88 ***Randomized, Open-Label, Phase 3 Clinical Study in Relapsed Multiple Myeloma***

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

95 Stratification factors were based on the number of lines of prior therapy the patient had  
96 previously received (1 previous line versus more than 1 line of therapy), time of progression  
97 relative to prior treatment (progression during or within 6 months of stopping their most recent  
98 therapy versus relapse >6 months after receiving their most recent therapy), and screening  
99 β<sub>2</sub>-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).

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

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102

**Table 1: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Multiple Myeloma Study**

<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%
<b>Previous Therapy</b>		
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%

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

110 Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles  
 111 followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone  
 112 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a  
 113 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone  
 114 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period  
 115 (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered  
 116 VELCADE at a standard dose and schedule on a companion study.

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

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

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

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

**Table 2: Summary of Efficacy Analyses in the Phase 3 Multiple Myeloma Study**

Efficacy Endpoint	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	Dex	VELCADE	Dex	VELCADE	Dex
	n=333	n=336	n=132	n=119	n=200	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 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (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

137 <sup>a</sup> Kaplan-Meier estimate.

138 <sup>b</sup> Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A  
139 hazard ratio less than 1 indicates an advantage for VELCADE.

140 <sup>c</sup> p-value based on the stratified log-rank test including randomization stratification factors.

141 <sup>d</sup> Precise p-value cannot be rendered.

142 <sup>e</sup> Response population includes patients who had measurable disease at baseline and received at least 1 dose of  
143 study drug.

144 <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  
145 category.

146 <sup>g</sup> In 2 patients, the IF was unknown.

147 <sup>h</sup> p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the  
148 stratification factors;

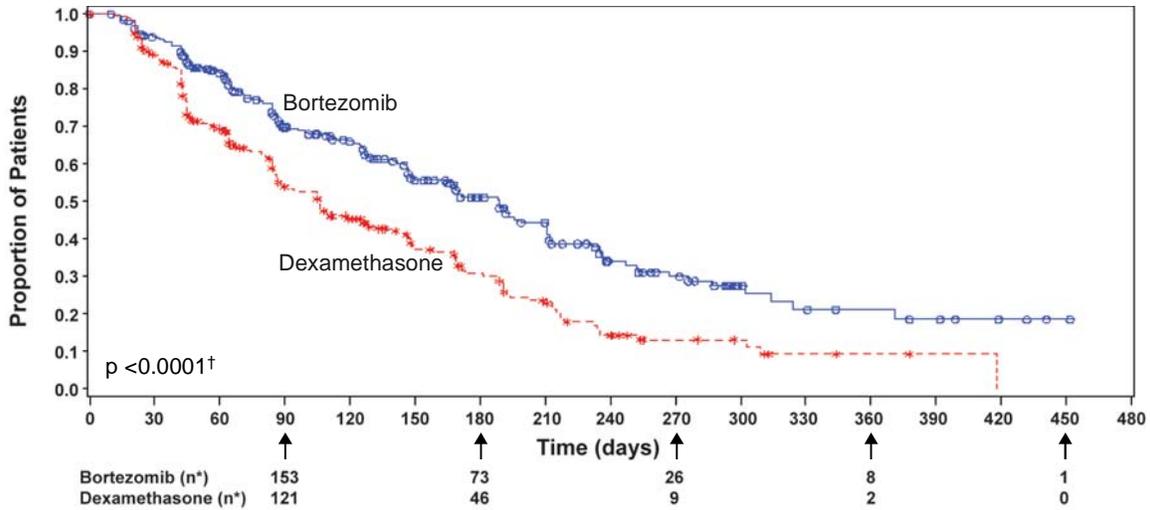
149 <sup>i</sup> Not Estimable.

150 <sup>j</sup> Not Applicable, no patients in category.

151 TTP was statistically significantly longer on the VELCADE arm (see **Figure 1**).

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



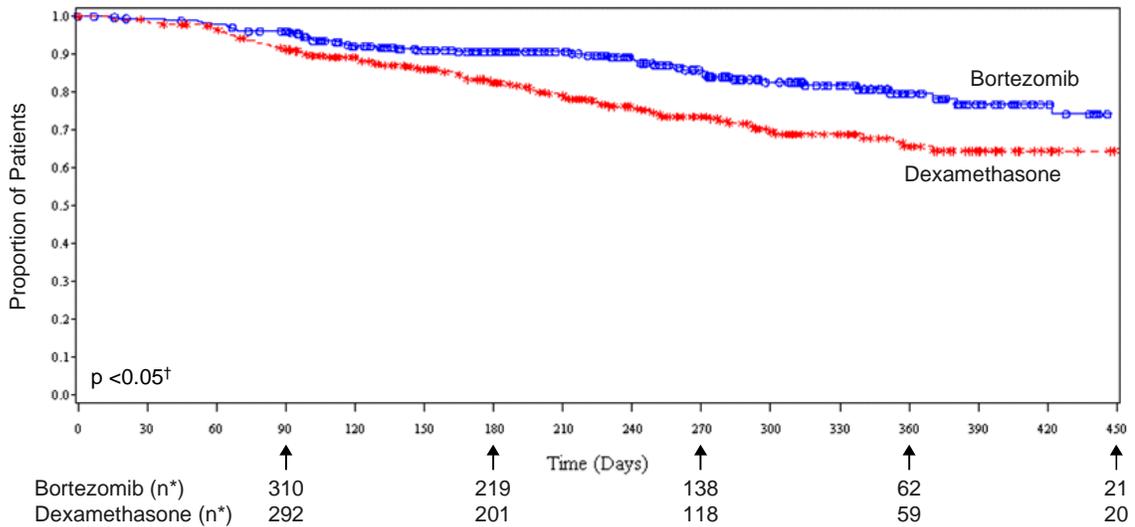
\* Patients remaining after the indicated timepoint  
† p-value from log-rank test

154

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

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



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

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160 For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median  
161 duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2

162 months) for the 56 responders on the dexamethasone arm. The response rate was significantly  
 163 higher on the VELCADE arm regardless of  $\beta_2$ -microglobulin levels at baseline.

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

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

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

174 **Table 3: Summary of Baseline Patient and Disease Characteristics**  
 175 **in a Phase 2 Multiple Myeloma Study\***

<b>Patient Characteristics</b>	<b>N = 202</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 x 10 <sup>9</sup> /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%

176 \* Based on number of patients with baseline data available

177 Responses to VELCADE alone are shown in **Table 4**. Response rates to VELCADE alone were  
 178 determined by an independent review committee (IRC) based on EBMT criteria.<sup>1</sup> Response  
 179 rates using the Southwest Oncology Group (SWOG) criteria<sup>2</sup> are also shown. SWOG response  
 180 required a  $\geq 75\%$  reduction in serum myeloma protein and/or  $\geq 90\%$  urine protein. A total of 188  
 181 patients were evaluable for response; 9 patients with nonmeasurable disease could not be

182 evaluated for response by the IRC, and 5 patients were excluded from the efficacy analyses  
 183 because they had had minimal prior therapy. The mean number of cycles administered was 6.  
 184 The median time to response was 38 days (range 30 to 127 days). The median survival of all  
 185 patients enrolled was 17 months (range <1 to 36+ months).

186 **Table 4: Summary of Response Outcomes in a Phase 2 Multiple Myeloma Study**

<b>Response Analyses (VELCADE monotherapy) 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)

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

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

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

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

197 An open-label, multicenter study randomized 54 patients with multiple myeloma who had  
 198 progressed or relapsed on or after front-line therapy to receive VELCADE 1.0 mg/m<sup>2</sup> or  
 199 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-day rest  
 200 period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma  
 201 and first dose of VELCADE on this trial was 2.0 years, and patients had received a median of 1  
 202 prior line of treatment (median of 3 prior therapies). A single complete response was seen at  
 203 each dose. The overall response rates (CR + PR) were 30% (8/27) at 1.0 mg/m<sup>2</sup> and 38% (10/26)  
 204 at 1.3 mg/m<sup>2</sup>.

205 ***A Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma***

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

216 ***A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma After Prior therapy***  
 217 The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were  
 218 evaluated in an open-label, single-arm, multicenter study of 155 patients with progressive disease  
 219 who had received at least 1 prior therapy. The median age of the patients was 65 years (42, 89),  
 220 81% were male, and 92% were caucasian. Of the total, 75% had one or more extra-nodal sites of  
 221 disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the  
 222 following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty  
 223 seven percent (37%) of patients were refractory to their last prior therapy. An IV bolus injection  
 224 of VELCADE 1.3 mg/m<sup>2</sup>/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and  
 225 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. The  
 226 study employed dose modifications for toxicity (see **DOSAGE AND ADMINISTRATION**).

227 Responses to VELCADE are shown in **Table 5**. Response rates to VELCADE were determined  
 228 according to the International Workshop Criteria (IWRC)<sup>3</sup> based on independent radiologic  
 229 review of CT scans. The median number of cycles administered across all patients was 4; in  
 230 responding patients the median number of cycles was 8. The median time to response was 40  
 231 days (range 31 to 204 days). The median duration of follow-up was more than 13 months.

232 **Table 5: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study**

<b>Response Analyses (N = 155)</b>	<b>N (%)</b>	<b>95% CI</b>
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
<b>Duration of Response</b>	<b>Median</b>	<b>95% CI</b>
CR + CRu + PR (N = 48)	9.3 months	(5.4, 13.8)
CR + CRu (N = 12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)

233 **INDICATIONS AND USAGE**

234 VELCADE<sup>®</sup> (bortezomib) for Injection is indicated for the treatment of patients with multiple  
 235 myeloma who have received at least 1 prior therapy.

236 VELCADE<sup>®</sup> (bortezomib) for Injection is indicated for the treatment of patients with mantle cell  
 237 lymphoma who have received at least 1 prior therapy.

238 **CONTRAINDICATIONS**

239 VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or  
 240 mannitol.

241 **WARNINGS**

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

244 ***Pregnancy Category D***

245 Women of childbearing potential should avoid becoming pregnant while being treated with  
246 VELCADE.

247 Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits  
248 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 mg/m<sup>2</sup> in the  
249 rabbit) when administered during organogenesis. These dosages are approximately half the  
250 clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

251 Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m<sup>2</sup>)  
252 experienced significant post-implantation loss and decreased number of live fetuses. Live  
253 fetuses from these litters also showed significant decreases in fetal weight. The dose is  
254 approximately 0.5 times the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

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

259 **PRECAUTIONS**

260 ***Peripheral Neuropathy:*** VELCADE treatment causes a peripheral neuropathy that is  
261 predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have  
262 been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the  
263 feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral  
264 neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be  
265 monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia,  
266 hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new  
267 or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE  
268 (see **DOSAGE AND ADMINISTRATION**). Following dose adjustments, improvement in or  
269 resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral  
270 neuropathy in the phase 3 multiple myeloma study. Improvement in or resolution of peripheral  
271 neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who  
272 had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies (**also see**  
273 **ADVERSE REACTIONS**). The long-term outcome of peripheral neuropathy has not been  
274 studied in mantle cell lymphoma.

275 ***Hypotension:*** The incidence of hypotension (postural, orthostatic, and hypotension NOS) was  
276 13%. These events are observed throughout therapy. Caution should be used when treating  
277 patients with a history of syncope, patients receiving medications known to be associated with  
278 hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension  
279 may include adjustment of antihypertensive medications, hydration, and administration of  
280 mineralocorticoids and/or sympathomimetics (see **ADVERSE REACTIONS**).

281 ***Cardiac Disorders:*** Acute development or exacerbation of congestive heart failure, and/or new  
282 onset of decreased left ventricular ejection fraction has been reported, including reports in  
283 patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with  
284 risk factors for, or existing heart disease should be closely monitored. In the phase 3 multiple  
285 myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in  
286 the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events

287 (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock,  
288 pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%,  
289 respectively. There have been isolated cases of QT-interval prolongation in clinical studies;  
290 causality has not been established.

291 ***Pulmonary Disorders:*** There have been rare reports of acute diffuse infiltrative pulmonary  
292 disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and  
293 Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these  
294 events have been fatal. A higher proportion of these events have been reported in Japan.

295 In a clinical trial, the first two patients given high-dose cytarabine (2g/m<sup>2</sup> per day) by continuous  
296 infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of  
297 ARDS early in the course of therapy.

298 There have been rare reports of pulmonary hypertension associated with VELCADE  
299 administration in the absence of left heart failure or significant pulmonary disease.

300 In the event of new or worsening cardiopulmonary symptoms, a prompt comprehensive  
301 diagnostic evaluation should be conducted.

302 ***Reversible Posterior Leukoencephalopathy Syndrome (RPLS):*** There have been rare reports of  
303 RPLS in patients receiving VELCADE. RPLS is a rare, reversible, neurological disorder which  
304 can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual  
305 and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging),  
306 is used to confirm the diagnosis. In patients developing RPLS, discontinue VELCADE. The  
307 safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known.

308 ***Laboratory Tests:*** Complete blood counts (CBC) should be frequently monitored during  
309 treatment with VELCADE.

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

314 ***Thrombocytopenia/Neutropenia:*** VELCADE is associated with thrombocytopenia and  
315 neutropenia (see **ADVERSE REACTIONS**). Platelets and neutrophils were lowest at Day 11 of  
316 each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. The  
317 cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8  
318 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or  
319 neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The  
320 severity of thrombocytopenia related to pretreatment platelet count is shown in **Table 6**. In the  
321 phase 3 multiple myeloma study, the incidence of significant bleeding events ( $\geq$ Grade 3) was  
322 similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be  
323 monitored prior to each dose of VELCADE. VELCADE therapy should be held when the  
324 platelet count is  $<25,000/\mu\text{L}$  and reinitiated at a reduced dose (see **DOSAGE AND**  
325 **ADMINISTRATION and ADVERSE REACTIONS**). There have been reports of  
326 gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may  
327 be considered. The incidence of febrile neutropenia was  $<1\%$ .

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**Table 6: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Phase 3 Myeloma 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%)

330 \* A baseline platelet count of 50,000/ $\mu$ L was required for study eligibility.

331 \*\* Data were missing at baseline for 1 patient

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

### 336 **Hepatic Events**

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

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

346 **Patients with Renal Impairment:** Patients with renal impairment should be closely monitored  
347 for toxicities when treated with VELCADE (see **CLINICAL**  
348 **PHARMACOLOGY/Pharmacokinetics-Special Populations**).

### 349 **Animal Toxicity Findings**

#### 350 **Cardiovascular Toxicity**

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

#### 357 **Chronic Administration**

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

364 ***Information for Patients***

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

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

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

374 ***Drug Interactions***

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

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

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

385 ***Drug Laboratory Test Interactions***

386 None known.

387 ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

388 Carcinogenicity studies have not been conducted with bortezomib.

389 Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the in vitro  
390 chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not  
391 genotoxic when tested in the in vitro mutagenicity assay (Ames test) and in vivo micronucleus  
392 assay in mice.

393 Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has  
394 been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative  
395 effects in the ovary were observed at doses  $\geq 0.3$  mg/m<sup>2</sup> (one-fourth of the recommended clinical  
396 dose), and degenerative changes in the testes occurred at 1.2 mg/m<sup>2</sup>. VELCADE could have a  
397 potential effect on either male or female fertility.

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

399 ***Pregnancy***

400 Patients should be advised to use effective contraceptive measures to prevent pregnancy.

401 ***Nursing Mothers***

402 It is not known whether bortezomib is excreted in human milk. Because many drugs are  
403 excreted in human milk and because of the potential for serious adverse reactions in nursing

404 infants from VELCADE, women should be advised against breast feeding while being treated  
405 with VELCADE.

#### 406 *Pediatric Use*

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

#### 408 *Geriatric Use*

409 Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of  
410 age or older: 125 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm. Median  
411 time to progression and median duration of response for patients  $\geq 65$  were longer on VELCADE  
412 compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively].

413 On the VELCADE arm, 40% (n=46) of evaluable patients aged  $\geq 65$  experienced response  
414 (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events  
415 was 64%, 78% and 75% for VELCADE patients  $\leq 50$ , 51-64 and  $\geq 65$  years old, respectively (**see**  
416 **CLINICAL STUDIES**).

417 In the phase 2 clinical study of 202 patients with relapsed multiple myeloma, 35% of patients  
418 were 65 years of age or older, the incidence of Grade  $\geq 3$  events was 74%, 80%, and 85% for  
419 VELCADE patients  $\leq 50$ , 51 to 65, and  $>65$  years old, respectively (**see CLINICAL STUDIES**).

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

## 423 **ADVERSE REACTIONS**

### 424 *Randomized Open-Label Phase 3 Multiple Myeloma Study*

425 Among the 331 VELCADE treated patients, the most commonly reported events overall were  
426 asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%), peripheral  
427 neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric disorders (each  
428 35%), anorexia and appetite decreased (34%), paresthesia and dysesthesia (27%), anemia and  
429 headache (each 26%), and cough (21%). The most commonly reported adverse events reported  
430 among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic  
431 conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung  
432 infections (each 21%). Fourteen percent (14%) of patients in the VELCADE treated arm  
433 experienced a Grade 4 adverse event; the most common toxicities were thrombocytopenia (4%),  
434 neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%) of dexamethasone treated  
435 patients experienced a Grade 4 adverse event; the most common toxicity was hyperglycemia  
436 (2%).

### 437 *Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the* 438 *Phase 3 Multiple Myeloma Study*

439 Serious adverse events are defined as any event, regardless of causality, that results in death, is  
440 life-threatening, requires hospitalization or prolongs a current hospitalization, results in a  
441 significant disability, or is deemed to be an important medical event. A total of 144 (44%)  
442 patients from the VELCADE treatment arm experienced an SAE during the study, as did 144  
443 (43%) dexamethasone-treated patients. The most commonly reported SAEs in the VELCADE  
444 treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting

445 (3%). In the dexamethasone treatment group, the most commonly reported SAEs were  
446 pneumonia (7%), pyrexia (4%), and hyperglycemia (3%).

447 A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment group  
448 and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from  
449 treatment due to adverse events assessed as drug-related by the investigators. Among the  
450 331 VELCADE treated patients, the most commonly reported drug-related event leading to  
451 discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone  
452 group, the most commonly reported drug-related events leading to treatment discontinuation  
453 were psychotic disorder and hyperglycemia (2% each).

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

458 ***Most Commonly Reported Adverse Events in the Phase 3 Multiple Myeloma Study***

459 The most common adverse events from the phase 3 multiple myeloma study are shown in  
460 **Table 7**. All adverse events with incidence  $\geq 10\%$  in the VELCADE arm are included.

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**Table 7: Most Commonly Reported Adverse Events (≥10% in VELCADE arm), with Grades 3 and 4 Intensity in the Phase 3 Multiple Myeloma 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)	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

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<sup>a</sup> 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).

466 ***The Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma***  
467 In the phase 2 extension study of 63 patients noted above (see **CLINICAL STUDIES**) no new  
468 cumulative or new long-term toxicities were observed with prolonged VELCADE treatment.

469 ***Integrated Summary of Safety (Multiple Myeloma and Mantle Cell Lymphoma)***  
470 Safety data from phase 2 and 3 studies of VELCADE 1.3 mg/m<sup>2</sup>/dose twice weekly for 2 weeks  
471 followed by a 10-day rest period in 1163 patients with multiple myeloma (N=1008) and mantle  
472 cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of  
473 VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

474 In the integrated analysis, the most commonly reported adverse events were asthenic conditions  
475 (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation  
476 (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral  
477 neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia)  
478 (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty percent (20%) of  
479 patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia  
480 (5%) and neutropenia (3%).

481 ***Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the***  
482 ***Integrated Summary of Safety***

483 A total of 50% of patients experienced SAEs during the studies. The most commonly reported  
484 SAEs included pneumonia (7%), pyrexia (6%), diarrhea (5%), vomiting (4%), and nausea,  
485 dehydration, dyspnea and thrombocytopenia (each 3%).

486 Adverse events thought by the investigator to be drug-related and leading to discontinuation  
487 occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy  
488 (8%), asthenic conditions (3%) and thrombocytopenia and diarrhea (each 2%).

489 In total, 2% of the patients died and the cause of death was considered by the investigator to be  
490 possibly related to study drug: including reports of cardiac arrest, congestive heart failure,  
491 respiratory failure, renal failure, pneumonia and sepsis.

492 ***Most Commonly Reported Adverse Events in the Integrated Summary of Safety***

493 The most common adverse events are shown in **Table 8**. All adverse events occurring at ≥10%  
494 are included. In the absence of a randomized comparator arm, it is often not possible to  
495 distinguish between adverse events that are drug-caused and those that reflect the patient's  
496 underlying disease. Please see the discussion of specific adverse reactions that follows.

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**Table 8: Most Commonly Reported (≥10% Overall) Adverse Events in Integrated Analyses of Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m<sup>2</sup> Dose (N=1163)**

Adverse Events	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
	All Events	≥Grade 3	All Events	≥Grade 3	All Events	≥Grade 3
Asthenic conditions	740 (64)	189 (16)	628 (62)	160 (16)	112 (72)	29 (19)
Nausea	640 (55)	43 (4)	572 (57)	39 (4)	68 (44)	4 (3)
Diarrhea	604 (52)	96 (8)	531 (53)	85 (8)	73 (47)	11 (7)
Constipation	481 (41)	26 (2)	404 (40)	22 (2)	77 (50)	4 (3)
Peripheral neuropathy <sup>a</sup>	457 (39)	134 (12)	372 (37)	114 (11)	85 (55)	20 (13)
Thrombocytopenia	421 (36)	337 (29)	388 (38)	320 (32)	33 (21)	17 (11)
Appetite decreased	417 (36)	30 (3)	357 (35)	25 (2)	60 (39)	5 (3)
Pyrexia	401 (34)	36 (3)	371 (37)	34 (3)	30 (19)	2 (1)
Vomiting	385 (33)	57 (5)	343 (34)	53 (5)	42 (27)	4 (3)
Anemia	333 (29)	124 (11)	306 (30)	120 (12)	27 (17)	4 (3)
Edema	262 (23)	10 (<1)	218 (22)	6 (<1)	44 (28)	4 (3)
Paresthesia and dysesthesia	254 (22)	16 (1)	240 (24)	14 (1)	14 (9)	2 (1)
Headache	253 (22)	17 (1)	227 (23)	17 (2)	26 (17)	0
Dyspnea	244 (21)	59 (5)	209 (21)	52 (5)	35 (23)	7 (5)
Cough	232 (20)	5 (<1)	202 (20)	5 (<1)	30 (19)	0
Insomnia	232 (20)	7 (<1)	199 (20)	6 (<1)	33 (21)	1 (<1)
Rash	213 (18)	10 (<1)	170 (17)	6 (<1)	43 (28)	4 (3)
Arthralgia	199 (17)	27 (2)	179 (18)	25 (2)	20 (13)	2 (1)
Neutropenia	195 (17)	143 (12)	185 (18)	137 (14)	10 (6)	6 (4)
Dizziness (excluding vertigo)	195 (17)	18 (2)	159 (16)	13 (1)	36 (23)	5 (3)
Pain in limb	179 (15)	36 (3)	172 (17)	36 (4)	7 (5)	0
Abdominal pain	170 (15)	30 (3)	146 (14)	22 (2)	24 (15)	8 (5)
Bone pain	166 (14)	37 (3)	163 (16)	37 (4)	3 (2)	0
Back pain	151 (13)	39 (3)	150 (15)	39 (4)	1 (<1)	0
Hypotension	147 (13)	37 (3)	124 (12)	32 (3)	23 (15)	5 (3)
Herpes zoster	145 (12)	22 (2)	131 (13)	21 (2)	14 (9)	1 (<1)
Nasopharyngitis	139 (12)	2 (<1)	126 (13)	2 (<1)	13 (8)	0
Upper respiratory tract infection	138 (12)	2 (<1)	114 (11)	1 (<1)	24 (15)	1 (<1)
Myalgia	136 (12)	9 (<1)	121 (12)	9 (<1)	15 (10)	0
Pneumonia	134 (12)	72 (6)	120 (12)	65 (6)	14 (9)	7 (5)
Muscle cramps	125 (11)	1 (<1)	118 (12)	1 (<1)	7 (5)	0
Dehydration	120 (10)	40 (3)	109 (11)	33 (3)	11 (7)	7 (5)
Anxiety	118 (10)	6 (<1)	111 (11)	6 (<1)	7 (5)	0

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<sup>a</sup> 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).

503 **Description of Selected Adverse Events from the Phase 2 and 3 Multiple Myeloma and**  
504 **Phase 2 Mantle Cell Lymphoma Studies**

505 ***Gastrointestinal Events***

506 A total of 87% of patients experienced at least one GI disorder. The most common GI disorders  
507 included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders  
508 included dyspepsia and dysgeusia. Grade 3 GI events occurred in 18% of patients; Grade 4  
509 events were rare (1%). GI events were considered serious in 11% of patients. Five percent (5%)  
510 of patients discontinued due to a GI event. Nausea was reported more often in patients with  
511 multiple myeloma (57%) compared to patients with mantle cell lymphoma (44%) (**see**  
512 **PRECAUTIONS**).

513 ***Thrombocytopenia***

514 Across the studies, VELCADE associated thrombocytopenia was characterized by a decrease in  
515 platelet count during the dosing period (days 1 to 11) and a return toward baseline during the 10-  
516 day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 36% of  
517 patients. Thrombocytopenia was Grade 3 in 24%,  $\geq$ Grade 4 in 5%, and serious in 3% of  
518 patients, and the event resulted in VELCADE discontinuation in 2% of patients (**see**  
519 **PRECAUTIONS**). Thrombocytopenia was reported more often in patients with multiple  
520 myeloma (38%) compared to patients with mantle cell lymphoma (21%). The incidence of  
521  $\geq$ Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (32%) compared  
522 to patients with mantle cell lymphoma (11%).

523 ***Peripheral Neuropathy***

524 Overall, peripheral neuropathy NEC occurred in 39% of patients. Peripheral neuropathy was  
525 Grade 3 for 11% of patients and Grade 4 for <1% of patients. Eight percent (8%) of patients  
526 discontinued VELCADE due to peripheral neuropathy. The incidence of peripheral neuropathy  
527 was higher among patients with mantle cell lymphoma (55%) compared to patients with multiple  
528 myeloma (37%).

529 In the phase 3 multiple myeloma study, among the 87 patients who experienced  $\geq$  Grade 2  
530 peripheral neuropathy, 51% had improved or resolved with a median of 3.5 months from first  
531 onset.

532 Among the patients with peripheral neuropathy in the phase 2 multiple myeloma studies that was  
533 Grade 2 and led to discontinuation or was  $\geq$ Grade 3, 73% (24 of 33) reported improvement or  
534 resolution following VELCADE dose adjustment, with a median time to improvement of one  
535 Grade or more from the last dose of VELCADE of 33 days (**see PRECAUTIONS**).

536 ***Hypotension***

537 The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension  
538 NOS) was 13% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the  
539 majority of patients and Grade 3 in 3% and  $\geq$ Grade 4 in <1%. Three percent (3%) of patients  
540 had hypotension reported as an SAE, and 1% discontinued due to hypotension. The incidence of  
541 hypotension was similar in patients with multiple myeloma (12%) and those with mantle cell  
542 lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal  
543 event. Doses of antihypertensive medications may need to be adjusted in patients receiving  
544 VELCADE (**see PRECAUTIONS**).

545 ***Neutropenia***

546 Neutrophil counts decreased during the VELCADE dosing period (days 1 to 11) and returned  
547 toward baseline during the 10-day rest period during each treatment cycle. Overall, neutropenia  
548 occurred in 17% of patients and was Grade 3 in 9% of patients and ≥Grade 4 in 3%.

549 Neutropenia was reported as a serious event in <1% of patients and <1% of patients discontinued  
550 due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma  
551 (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥Grade 3  
552 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with  
553 mantle cell lymphoma (4%) (**see PRECAUTIONS**).

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

555 Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and  
556 ≥Grade 4 in <1% of patients. Four percent (4%) of patients discontinued treatment due to  
557 asthenia. Asthenic conditions were reported in 62% of patients with multiple myeloma and 72%  
558 of patients with mantle cell lymphoma.

559 ***Pyrexia***

560 Pyrexia (>38°C) was reported as an adverse event for 34% of patients. The event was Grade 3 in  
561 3% and ≥Grade 4 in <1%. Pyrexia was reported as a serious adverse event in 6% of patients and  
562 led to VELCADE discontinuation in <1% of patients. The incidence of pyrexia was higher  
563 among patients with multiple myeloma (37%) compared to patients with mantle cell lymphoma  
564 (19%). The incidence of ≥Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in  
565 patients with mantle cell lymphoma.

566 ***Reactivation of Herpes Virus Infection***

567 Reactivation of herpes virus infections, including herpes zoster and herpes simplex was reported  
568 in 13% and 7% of patients, respectively. This included ophthalmic herpes zoster and ophthalmic  
569 herpes simplex each in <1% of patients. Multidermatomal herpes zoster also has been reported.  
570 Herpes reactivation was reported as a serious event in 2% of patients and led to discontinuation  
571 of VELCADE in <1% of patients. In the phase 3 multiple myeloma study, herpes reactivation  
572 was more common in patients treated with VELCADE (13% herpes zoster, 8% herpes simplex)  
573 than in patients treated with dexamethasone (5% herpes zoster, 5% herpes simplex). In the  
574 postmarketing experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have  
575 been reported.

576 ***Additional Adverse Events from Clinical Studies and Post-Marketing***

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

581 ***Blood and lymphatic system disorders:*** Disseminated intravascular coagulation, lymphopenia,  
582 leukopenia

583 ***Cardiac disorders:*** Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia,  
584 sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia,  
585 myocardial infarction, pericarditis, pericardial effusion, Torsades de pointes, ventricular  
586 tachycardia

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

588 **Eye disorders:** Diplopia and blurred vision, conjunctival infection, irritation

589 **Gastrointestinal disorders:** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis  
590 hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction,  
591 paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal  
592 perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal  
593 reflux

594 **General disorders and administration site conditions:** Injection site erythema, neuralgia,  
595 injection site pain, irritation, phlebitis

596 **Hepatobiliary disorders:** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein  
597 thrombosis, hepatitis, liver failure

598 **Immune system disorders:** Anaphylactic reaction, drug hypersensitivity, immune complex  
599 mediated hypersensitivity, angioedema, laryngeal edema

600 **Infections and infestations:** Aspergillosis, bacteremia, urinary tract infection, herpes viral  
601 infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related  
602 infection

603 **Injury, poisoning and procedural complications:** Catheter related complication, skeletal  
604 fracture, subdural hematoma

605 **Metabolism and nutrition disorders:** Hypocalcemia, hyperuricemia, hypokalemia,  
606 hyperkalemia, hyponatremia, hypernatremia

607 **Nervous system disorders:** Ataxia, coma, dysarthria, dysautonomia, encephalopathy, cranial  
608 palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression,  
609 paralysis, postherpetic neuralgia, transient ischemic attack, reversible posterior  
610 leukoencephalopathy syndrome

611 **Psychiatric disorders:** Agitation, confusion, mental status change, psychotic disorder, suicidal  
612 ideation

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

616 **Respiratory, thoracic and mediastinal disorders:** Acute respiratory distress syndrome,  
617 aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia,  
618 dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion,  
619 pneumonitis, respiratory distress, pulmonary hypertension

620 **Skin and subcutaneous tissue disorders:** Urticaria, face edema, rash (which may be pruritic),  
621 leukocytoclastic vasculitis

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

624 **Post-Marketing Experience**  
625 Clinically significant adverse events are listed here if they have been reported during post-  
626 approval use of VELCADE and either they have not been reported in clinical trials, or they have

627 been reported in clinical trials, but their occurrence in the post-approval setting is considered  
628 meaningful:

629       Atrioventricular block complete, cardiac tamponade, ischemic colitis, encephalopathy,  
630       dysautonomia, deafness bilateral, disseminated intravascular coagulation, hepatitis, acute  
631       pancreatitis, acute diffuse infiltrative pulmonary disease and toxic epidermal necrolysis.

## 632 **OVERDOSAGE**

633 There is no known specific antidote for VELCADE overdose (**see PRECAUTIONS and**  
634 **DOSAGE AND ADMINISTRATION**). In humans, fatal outcomes following the  
635 administration of more than twice the recommended therapeutic dose have been reported, which  
636 were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the  
637 event of an overdose, the patient's vital signs should be monitored and appropriate supportive  
638 care given.

639 Studies in monkeys and dogs showed that IV bortezomib doses as low as 2 times the  
640 recommended clinical dose on a  $\text{mg}/\text{m}^2$  basis were associated with increases in heart rate,  
641 decreases in contractility, hypotension, and death. In dog studies, a slight increase in the  
642 corrected QT interval was observed at doses resulting in death. In monkeys, doses of  $3.0 \text{ mg}/\text{m}^2$   
643 and greater (approximately twice the recommended clinical dose) resulted in hypotension  
644 starting at 1 hour post-administration, with progression to death in 12 to 14 hours following drug  
645 administration.

## 646 **DOSAGE AND ADMINISTRATION**

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

### 654 *Dose Modification and Re-initiation of Therapy*

655 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade  
656 4 hematological toxicities excluding neuropathy as discussed below (**see PRECAUTIONS**).  
657 Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a  
658 25% reduced dose ( $1.3 \text{ mg}/\text{m}^2/\text{dose}$  reduced to  $1.0 \text{ mg}/\text{m}^2/\text{dose}$ ;  $1.0 \text{ mg}/\text{m}^2/\text{dose}$  reduced to  
659  $0.7 \text{ mg}/\text{m}^2/\text{dose}$ ).

660 **Table 9** contains the recommended dose modification for the management of patients who  
661 experience VELCADE related neuropathic pain and/or peripheral neuropathy. Patients with  
662 preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit  
663 assessment.

664  
665

**Table 9: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy**

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias, weakness 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 reinstate with a reduced dose of VELCADE at 0.7 mg/m <sup>2</sup> and change treatment schedule to once per week.
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE

666 Grading based on NCI Common Toxicity Criteria CTCAE v3.0

667 **Administration Precautions:** VELCADE is an antineoplastic. Caution should be used during  
668 handling and preparation including careful dose calculation to prevent overdose. The drug  
669 quantity contained in one vial (3.5 mg) may exceed the usual single dose required. Proper  
670 aseptic technique should be used. Use of gloves and other protective clothing to prevent skin  
671 contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients,  
672 but extravasation of VELCADE was not associated with tissue damage.

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

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

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

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

#### 687 **HOW SUPPLIED**

688 VELCADE<sup>®</sup> (bortezomib) for Injection is supplied as individually cartoned 10 mL vials  
689 containing 3.5 mg of bortezomib as a white to off-white cake or powder.

690 NDC 63020-049-01

691 3.5 mg single dose vial

692 **STORAGE**

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

696 **Caution: R<sub>x</sub> only**

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

698 ***Distributed and Marketed by:***

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

719 **PATIENT INFORMATION**

720 VELCADE is intended for use under the guidance and supervision of a healthcare professional.

721 Please discuss the possibility of the following side effects with your doctor:

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

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

726 ***Pregnancy/Nursing:***

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

733 ***Dehydration/Hypotension:***

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

739 ***Concomitant Medications:***

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

742 ***Diabetic Patients:***

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

745 ***Peripheral Neuropathy:***

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

749 ***Herpes zoster (Shingles):***

750 Contact your doctor if you develop a rash.

751 ***Heart Failure and Lung Disease:***

752 Contact your doctor if you experience shortness of breath, cough, or swelling of the feet, ankles,  
753 or legs.

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