

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**  
2 **These highlights do not include all the information needed to use**  
3 **VELCADE safely and effectively. See full prescribing information**  
4 **for VELCADE.**  
5  
6 **VELCADE® (bortezomib) for Injection**  
7 **Initial U.S. Approval: 2003**  
8 -----**RECENT MAJOR CHANGES**-----  
9 Dosage and Administration (2.5) 12/2009  
10 Warnings and Precautions, Hepatic Impairment (5.11) 12/2009  
11 Patients with Hepatic Impairment (8.7) 12/2009  
12 Clinical Studies, Multiple Myeloma (14.1) 12/2009  
13 -----**INDICATIONS AND USAGE**-----  
14 VELCADE is a proteasome inhibitor indicated for:  
15 • treatment of patients with multiple myeloma (1.1)  
16 • treatment of patients with mantle cell lymphoma who have received at  
17 least 1 prior therapy (1.2)  
18 -----**DOSAGE AND ADMINISTRATION**-----  
19 The recommended dose of VELCADE is 1.3 mg/m<sup>2</sup> administered as a 3  
20 to 5 second bolus intravenous injection. (2.1, 2.3)  
21 Dose adjustment may be used to manage adverse events that occur  
22 during treatment (2.2, 2.4)  
23 -----**DOSAGE FORMS AND STRENGTHS**-----  
24 • 1 single use vial contains 3.5 mg of bortezomib. Dose must be  
25 individualized to prevent overdose. (3)  
26 -----**CONTRAINDICATIONS**-----  
27 • VELCADE is contraindicated in patients with hypersensitivity to  
28 bortezomib, boron, or mannitol. (4)  
29 -----**WARNINGS AND PRECAUTIONS**-----  
30 • Women should avoid becoming pregnant while being treated with  
31 VELCADE. Pregnant women should be apprised of the potential  
32 harm to the fetus. (5.1, 8.1)  
33 • Peripheral neuropathy, including severe cases, may occur - manage  
34 with dose modification or discontinuation. (2.2, 2.4) Patients with  
35 preexisting severe neuropathy should be treated with VELCADE only  
36 after careful risk-benefit assessment. (2.2, 2.4, 5.2)

71 **FULL PRESCRIBING INFORMATION: CONTENTS\***  
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37 • Hypotension can occur. Caution should be used when treating  
38 patients receiving antihypertensives, those with a history of syncope,  
39 and those who are dehydrated. (5.3)  
40 • Patients with risk factors for, or existing heart disease, should be  
41 closely monitored. (5.4)  
42 • Acute diffuse infiltrative pulmonary disease has been reported. (5.5)  
43 • Nausea, diarrhea, constipation, and vomiting have occurred and may  
44 require use of antiemetic and antidiarrheal medications or fluid  
45 replacement. (5.7)  
46 • Thrombocytopenia or neutropenia can occur; complete blood counts  
47 should be regularly monitored throughout treatment. (5.8)  
48 • Tumor Lysis Syndrome (5.9), Reversible Posterior  
49 Leukoencephalopathy Syndrome (5.6), and acute hepatic failure  
50 (5.10) have been reported.  
51 -----**ADVERSE REACTIONS**-----  
52 Most commonly reported adverse reactions (incidence ≥30%) in  
53 clinical studies include asthenic conditions, diarrhea, nausea,  
54 constipation, peripheral neuropathy, vomiting, pyrexia,  
55 thrombocytopenia, psychiatric disorders, anorexia and decreased  
56 appetite, neutropenia, neuralgia, leukopenia and anemia. Other  
57 adverse reactions, including serious adverse reactions, have been  
58 reported. (6.1)  
59 **To report SUSPECTED ADVERSE REACTIONS, contact**  
60 **Millennium Pharmaceuticals at 1-866 VELCADE or FDA at 1-**  
61 **800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**  
62 -----**USE IN SPECIFIC POPULATIONS**-----  
63 • Women should be advised against breast feeding or becoming  
64 pregnant while being treated with VELCADE. (5.1, 8.1, 8.3)  
65 • Patients with diabetes may require close monitoring of blood  
66 glucose and adjustment of anti-diabetic medication. (8.8)  
67 • Hepatic Impairment: In patients with moderate or severe hepatic  
68 impairment, use a lower starting dose (2.5, 5.11, 8.7, 12.3)  
69 **See 17 for PATIENT COUNSELING INFORMATION.**  
70 **Revised: [12/2009]**

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130 are not listed

131 **FULL PRESCRIBING INFORMATION**

132 **1 INDICATIONS AND USAGE**

133 **1.1 Multiple Myeloma**

134 VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple  
135 myeloma.

136 **1.2 Mantle Cell Lymphoma**

137 VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell  
138 lymphoma who have received at least 1 prior therapy.

139 **2 DOSAGE AND ADMINISTRATION**

140 **2.1 Dosage in Previously Untreated Multiple Myeloma**

141 VELCADE (bortezomib) is administered as a 3-5 second bolus IV injection in combination with  
142 oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1. In  
143 Cycles 1-4, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In  
144 Cycles 5-9, VELCADE is administered once weekly (days 1, 8, 22 and 29). At least 72 hours  
145 should elapse between consecutive doses of VELCADE.

146 **Table 1-Dosage Regimen for Patients with Previously Untreated Multiple Myeloma**

<b>Twice Weekly VELCADE (Cycles 1-4)</b>												
<b>Week</b>	<b>1</b>				<b>2</b>		<b>3</b>	<b>4</b>		<b>5</b>		<b>6</b>
VELCADE (1.3 mg/m <sup>2</sup> )	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan(9 mg/m <sup>2</sup> ) Prednisone(60 mg/m <sup>2</sup> )	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
<b>Once Weekly VELCADE (Cycles 5-9 when used in combination with Melphalan and Prednisone)</b>												
<b>Week</b>	<b>1</b>				<b>2</b>		<b>3</b>	<b>4</b>		<b>5</b>		<b>6</b>
VELCADE (1.3 mg/m <sup>2</sup> )	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan(9 mg/m <sup>2</sup> ) Prednisone(60 mg/m <sup>2</sup> )	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

147  
148 **2.2 Dose Modification Guidelines for Combination Therapy with VELCADE, Melphalan**  
149 **and Prednisone**

150 Prior to initiating any cycle of therapy with VELCADE in combination with melphalan and  
151 prednisone:

- 152 • Platelet count should be  $\geq 70 \times 10^9/L$  and the ANC should be  $\geq 1.0 \times 10^9/L$
- 153 • Non-hematological toxicities should have resolved to Grade 1 or baseline

154

155 **Table 2-Dose Modifications During Cycles of Combination VELCADE, Melphalan and**  
 156 **Prednisone Therapy**

Toxicity	Dose modification or delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count $\leq 30 \times 10^9/L$ or ANC $\leq 0.75 \times 10^9/L$ on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
If several VELCADE doses in consecutive cycles are withheld due to toxicity	VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m <sup>2</sup> to 1 mg/m <sup>2</sup> , or from 1 mg/m <sup>2</sup> to 0.7 mg/m <sup>2</sup> )
Grade $\geq 3$ non-hematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m <sup>2</sup> to 1 mg/m <sup>2</sup> , or from 1 mg/m <sup>2</sup> to 0.7 mg/m <sup>2</sup> ). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold or modify VELCADE as outlined in Table 3.

157 For information concerning melphalan and prednisone, see manufacturer's prescribing  
 158 information.

159

160 **2.3 Dosage in Relapsed Multiple Myeloma and Mantle Cell Lymphoma**

161 VELCADE (1.3 mg/m<sup>2</sup>/dose) is administered as a 3 to 5 second bolus intravenous injection  
 162 twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21).  
 163 For extended therapy of more than 8 cycles, VELCADE may be administered on the standard  
 164 schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22)  
 165 followed by a 13-day rest period (Days 23 to 35) [*see Clinical Studies section (14) for a*  
 166 *description of dose administration during the trials*]. At least 72 hours should elapse between  
 167 consecutive doses of VELCADE.

168 **2.4 Dose Modification Guidelines for Relapsed Multiple Myeloma and Mantle Cell**  
 169 **Lymphoma**

170 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade  
 171 4 hematological toxicities excluding neuropathy as discussed below [*see Warnings and*  
 172 *Precautions (5)*]. Once the symptoms of the toxicity have resolved, VELCADE therapy may be  
 173 reinitiated at a 25% reduced dose (1.3 mg/m<sup>2</sup>/dose reduced to 1 mg/m<sup>2</sup>/dose; 1 mg/m<sup>2</sup>/dose  
 174 reduced to 0.7 mg/m<sup>2</sup>/dose).

175 For the management of patients who experience VELCADE related neuropathic pain and/or  
 176 peripheral neuropathy see Table 3. Patients with preexisting severe neuropathy should be treated  
 177 with VELCADE only after careful risk-benefit assessment.

178  
179

**Table 3: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy**

<b>Severity of Peripheral Neuropathy Signs and Symptoms</b>	<b>Modification of Dose and Regimen</b>
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 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 reinstitute 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

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

181 **2.5 Dosage in Patients with Hepatic Impairment**

182 Patients with mild hepatic impairment do not require a starting dose adjustment and should be  
 183 treated per the recommended VELCADE dose. Patients with moderate or severe hepatic  
 184 impairment should be started on VELCADE at a reduced dose of 0.7 mg/m<sup>2</sup> per injection during  
 185 the first cycle, and a subsequent dose escalation to 1.0 mg/m<sup>2</sup> or further dose reduction to 0.5  
 186 mg/m<sup>2</sup> may be considered based on patient tolerance (see **Table 4**). [*see Warnings and*  
 187 *Precautions (5.11), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*]  
 188

189 **Table 4: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment**

	<b>Bilirubin Level</b>	<b>SGOT (AST) Levels</b>	<b>Modification of Starting Dose</b>
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x–1.5x ULN	Any	None
Moderate	> 1.5x–3x ULN	Any	Reduce VELCADE to 0.7 mg/m <sup>2</sup> in the first cycle. Consider dose escalation to 1.0 mg/m <sup>2</sup> or further dose reduction to 0.5 mg/m <sup>2</sup> in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

191 Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;  
 192 AST = aspartate aminotransferase; ULN = upper limit of the normal range.

193

194 **2.6 Administration Precautions**

195 The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution  
 196 should be used in calculating the dose to prevent overdose.

197 VELCADE is an antineoplastic. Procedures for proper handling and disposal should be  
198 considered. [*see How Supplied/Storage and Handling (16)*]

199 In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of  
200 VELCADE was not associated with tissue damage.

## 201 **2.7 Reconstitution/Preparation for Intravenous Administration**

202 Proper aseptic technique should be used. Reconstitute with 3.5 mL of 0.9% Sodium Chloride  
203 resulting in a final concentration of 1 mg/mL of bortezomib. The reconstituted product should  
204 be a clear and colorless solution.

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

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

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

## 216 **3 DOSAGE FORMS AND STRENGTHS**

217 Each single use vial of VELCADE contains 3.5 mg of bortezomib as a sterile lyophilized  
218 powder.

## 219 **4 CONTRAINDICATIONS**

220 VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or  
221 mannitol.

## 222 **5 WARNINGS AND PRECAUTIONS**

223 VELCADE should be administered under the supervision of a physician experienced in the use  
224 of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during  
225 treatment with VELCADE.

### 226 **5.1 Use in Pregnancy**

#### 227 **Pregnancy Category D**

228 Women of childbearing potential should avoid becoming pregnant while being treated with  
229 VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately  
230 0.5 times the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area caused post-implantation  
231 loss and a decreased number of live fetuses. [*see Use in Specific Populations (8.1)*]

### 232 **5.2 Peripheral Neuropathy**

233 VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However,  
234 cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-  
235 existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of  
236 peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3)

237 during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy,  
238 such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic  
239 pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require  
240 change in the dose and schedule of VELCADE [*see Dosage and Administration (2.2, 2.4)*].  
241 Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported  
242 in 51% of patients with  $\geq$ Grade 2 peripheral neuropathy in the relapsed multiple myeloma study.  
243 Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who  
244 discontinued due to Grade 2 neuropathy or who had  $\geq$ Grade 3 peripheral neuropathy in the phase  
245 2 multiple myeloma studies [*see Adverse Reactions (6)*]. The long-term outcome of peripheral  
246 neuropathy has not been studied in mantle cell lymphoma.

### 247 **5.3 Hypotension**

248 The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%. These  
249 events are observed throughout therapy. Caution should be used when treating patients with a  
250 history of syncope, patients receiving medications known to be associated with hypotension, and  
251 patients who are dehydrated. Management of orthostatic/postural hypotension may include  
252 adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids  
253 and/or sympathomimetics. [*see Adverse Reactions(6)*]

### 254 **5.4 Cardiac Disorders**

255 Acute development or exacerbation of congestive heart failure and new onset of decreased left  
256 ventricular ejection fraction have been reported, including reports in patients with no risk factors  
257 for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart  
258 disease should be closely monitored. In the relapsed multiple myeloma study, the incidence of  
259 any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and  
260 dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary  
261 edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was  
262 similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There have  
263 been isolated cases of QT-interval prolongation in clinical studies; causality has not been  
264 established.

### 265 **5.5 Pulmonary Disorders**

266 There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such  
267 as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress  
268 Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal.

269 In a clinical trial, the first two patients given high-dose cytarabine ( $2\text{g}/\text{m}^2$  per day) by continuous  
270 infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of  
271 ARDS early in the course of therapy.

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

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

### 276 **5.6 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

277 There have been reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible,  
278 neurological disorder which can present with seizure, hypertension, headache, lethargy,  
279 confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably

280 MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing  
 281 RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients  
 282 previously experiencing RPLS is not known.

### 283 5.7 Gastrointestinal Adverse Events

284 VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting [*see Adverse*  
 285 *Reactions (6)*] sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can  
 286 occur. Fluid and electrolyte replacement should be administered to prevent dehydration.

### 287 5.8 Thrombocytopenia/Neutropenia

288 VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern  
 289 with nadirs occurring following the last dose of each cycle and typically recovering prior to  
 290 initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and  
 291 recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no  
 292 evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir  
 293 measured was approximately 40% of baseline. The severity of thrombocytopenia related to  
 294 pretreatment platelet count is shown in **Table 5**. In the relapsed multiple myeloma study, the  
 295 incidence of significant bleeding events ( $\geq$ Grade 3) was similar on both the VELCADE (4%) and  
 296 dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of VELCADE.  
 297 Patients experiencing thrombocytopenia may require change in the dose and schedule of  
 298 VELCADE [*see Table 2 and Dosage and Administration (2.4)*]. There have been reports of  
 299 gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may  
 300 be considered. The incidence of febrile neutropenia was  $<1\%$ .

301 **Table 5: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the**  
 302 **Relapsed Multiple Myeloma Study**

Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count $<10,000/\mu\text{L}$	Number (%) of Patients with Platelet Count $10,000\text{-}25,000/\mu\text{L}$
$\geq 75,000/\mu\text{L}$	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%)

303 \* A baseline platelet count of  $50,000/\mu\text{L}$  was required for study eligibility

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

### 305 5.9 Tumor Lysis Syndrome

306 Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells, the complications  
 307 of tumor lysis syndrome may occur. Patients at risk of tumor lysis syndrome are those with high  
 308 tumor burden prior to treatment. These patients should be monitored closely and appropriate  
 309 precautions taken.

### 310 5.10 Hepatic Events

311 Cases of acute liver failure have been reported in patients receiving multiple concomitant  
 312 medications and with serious underlying medical conditions. Other reported hepatic events  
 313 include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be

314 reversible upon discontinuation of VELCADE. There is limited re-challenge information in  
315 these patients.

### 316 **5.11 Patients with Hepatic Impairment:**

317 Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with  
318 moderate or severe hepatic impairment; these patients should be treated with VELCADE at  
319 reduced starting doses and closely monitored for toxicities. [*see Dosage and Administration*  
320 (2.5), *Use In Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)]

## 321 **6 ADVERSE REACTIONS**

322 The following adverse reactions are also discussed in other sections of the labeling:

- 323 • Peripheral Neuropathy [*see Warnings and Precautions* (5.2); *Dosage and*  
324 *Administration* (Table 3)]
- 325 • Hypotension [*see Warnings and Precautions* (5.3)]
- 326 • Cardiac Disorders [*see Warnings and Precautions* (5.4)]
- 327 • Pulmonary Disorders [*see Warnings and Precautions* (5.5)]
- 328 • Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and*  
329 *Precautions* (5.6)]
- 330 • Gastrointestinal Adverse Events [*see Warnings and Precautions* (5.7)]
- 331 • Thrombocytopenia/Neutropenia [*see Warnings and Precautions* (5.8)]
- 332 • Tumor Lysis Syndrome [*see Warnings and Precautions* (5.9)]
- 333 • Hepatic Events [*see Warnings and Precautions* (5.10)]

### 334 **6.1 Clinical Trials Safety Experience**

335 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
336 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials  
337 of another drug and may not reflect the rates observed in practice.

#### 338 **Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma:**

339  
340 Table 6 describes safety data from 340 patients with previously untreated multiple myeloma who  
341 received VELCADE (1.3 mg/m<sup>2</sup>) in combination with melphalan (9 mg/m<sup>2</sup>) and prednisone  
342 (60 mg/m<sup>2</sup>) in a prospective randomized study.

343 The safety profile of VELCADE in combination with melphalan/prednisone is consistent with  
344 the known safety profiles of both VELCADE and melphalan/prednisone.

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**Table 6-Most Commonly Reported Adverse Events (≥ 10% in VELCADE, Melphalan and Prednisone arm) with Grades 3 and ≥4 Intensity in the Previously Untreated Multiple Myeloma Study**

MedDRA System Organ Class Preferred Term	VELCADE, Melphalan and Prednisone (N=340)			Melphalan and Prednisone (N=337)		
	Total n (%)	Toxicity Grade, n (%)		Total n (%)	Toxicity Grade, n (%)	
		3	≥4		3	≥4
<b>Blood and Lymphatic System Disorders</b>						
Thrombocytopenia	178 ( 52)	68 ( 20)	59 ( 17)	159 ( 47)	55 ( 16)	47 ( 14)
Neutropenia	165 ( 49)	102 ( 30)	35 ( 10)	155 ( 46)	79 ( 23)	49 ( 15)
Anemia	147 ( 43)	53 ( 16)	9 ( 3)	187 ( 55)	66 ( 20)	26 ( 8)
Leukopenia	113 ( 33)	67 ( 20)	10 ( 3)	100 ( 30)	55 ( 16)	13 ( 4)
Lymphopenia	83 ( 24)	49 ( 14)	18 ( 5)	58 ( 17)	30 ( 9)	7 ( 2)
<b>Gastrointestinal Disorders</b>						
Nausea	164 ( 48)	14 ( 4)	0	94 ( 28)	1 (<1)	0
Diarrhea	157 ( 46)	23 ( 7)	2 ( 1)	58 ( 17)	2 ( 1)	0
Constipation	125 ( 37)	2 ( 1)	0	54 ( 16)	0	0
Vomiting	112 ( 33)	14 ( 4)	0	55 ( 16)	2 ( 1)	0
Abdominal Pain	49 ( 14)	7 ( 2)	0	22 ( 7)	1 (<1)	0
Abdominal Pain Upper	40 ( 12)	1 (<1)	0	29 ( 9)	0	0
Dyspepsia	39 ( 11)	0	0	23 ( 7)	0	0
<b>Nervous System Disorders</b>						
Peripheral Neuropathy	159 ( 47)	43 ( 13)	2 ( 1)	18 ( 5)	0	0
Neuralgia	121 ( 36)	28 ( 8)	2 ( 1)	5 ( 1)	1 (<1)	0
Dizziness	56 ( 16)	7 ( 2)	0	37 ( 11)	1 (<1)	0
Headache	49 ( 14)	2 ( 1)	0	35 ( 10)	4 ( 1)	0
Paresthesia	45 ( 13)	6 ( 2)	0	15 ( 4)	0	0
<b>General Disorders and Administration Site Conditions</b>						
Pyrexia	99 ( 29)	8 ( 2)	2 ( 1)	64 ( 19)	6 ( 2)	2 ( 1)
Fatigue	98 ( 29)	23 ( 7)	2 ( 1)	86 ( 26)	7 ( 2)	0
Asthenia	73 ( 21)	20 ( 6)	1 (<1)	60 ( 18)	9 ( 3)	0
Edema Peripheral	68 ( 20)	2 ( 1)	0	34 ( 10)	0	0
<b>Infections and Infestations</b>						
Pneumonia	56 ( 16)	16 ( 5)	13 ( 4)	36 ( 11)	13 ( 4)	9 ( 3)
Herpes Zoster	45 ( 13)	11 ( 3)	0	14 ( 4)	6 ( 2)	0
Bronchitis	44 ( 13)	4 ( 1)	0	27 ( 8)	4 ( 1)	0
Nasopharyngitis	39 ( 11)	1 (<1)	0	27 ( 8)	0	0

**Musculoskeletal and Connective  
Tissue Disorders**

Back Pain	58 ( 17)	9 ( 3)	1 (<1)	62 ( 18)	11 ( 3)	1 (<1)
Pain In Extremity	47 ( 14)	8 ( 2)	0	32 ( 9)	3 ( 1)	1 (<1)
Bone Pain	37 ( 11)	7 ( 2)	1 (<1)	35 ( 10)	7 ( 2)	0
Arthralgia	36 ( 11)	4 ( 1)	0	50 ( 15)	2 ( 1)	1 (<1)

**Metabolism and Nutrition  
Disorders**

Anorexia	77 ( 23)	9 ( 3)	1 (<1)	34 ( 10)	4 ( 1)	0
Hypokalemia	44 ( 13)	19 ( 6)	3 ( 1)	25 ( 7)	8 ( 2)	2 ( 1)

**Skin and Subcutaneous Tissue  
Disorders**

Rash	66 ( 19)	2 ( 1)	0	24 ( 7)	1 (<1)	0
Pruritus	35 ( 10)	3 ( 1)	0	18 ( 5)	0	0

**Respiratory, Thoracic and  
Mediastinal Disorders**

Cough	71 ( 21)	0	0	45 ( 13)	2 ( 1)	0
Dyspnea	50 ( 15)	11 ( 3)	2 ( 1)	44 ( 13)	5 ( 1)	4 ( 1)

**Psychiatric Disorders**

Insomnia	69 ( 20)	1 (<1)	0	43 ( 13)	0	0
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**Vascular Disorders**

Hypertension	45 ( 13)	8 ( 2)	1 (<1)	25 ( 7)	2 ( 1)	0
Hypotension	41 ( 12)	4 ( 1)	3 ( 1)	10 ( 3)	2 ( 1)	2 ( 1)

350

351 **Relapsed Multiple Myeloma Randomized Study**

352 The safety data described below and in Table 7 reflect exposure to either VELCADE (n=331) or  
 353 dexamethasone (n=332) in a study of patients with multiple myeloma. VELCADE was  
 354 administered intravenously at doses of 1.3 mg/m<sup>2</sup> twice weekly for 2 out of 3 weeks (21 day  
 355 cycle). After eight 21-day cycles patients continued therapy for three 35-day cycles on a weekly  
 356 schedule. Duration of treatment was up to 11 cycles (9 months) with a median duration of 6  
 357 cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and 1  
 358 to 3 prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low  
 359 as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall  
 360 frequency of adverse events was similar in men and women, and in patients <65 and ≥65 years of  
 361 age. Most patients were Caucasian. [see *Clinical Studies (14.1)*]

362 Among the 331 VELCADE treated patients, the most commonly reported events overall were  
 363 asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%), peripheral  
 364 neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric disorders (each  
 365 35%), anorexia and appetite decreased (34%), paresthesia and dysesthesia (27%), anemia and  
 366 headache (each 26%), and cough (21%). The most commonly reported adverse events reported  
 367 among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic  
 368 conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung  
 369 infections (each 21%). Fourteen percent (14%) of patients in the VELCADE treated arm  
 370 experienced a Grade 4 adverse event; the most common toxicities were thrombocytopenia (4%),

371 neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%) of dexamethasone treated  
372 patients experienced a Grade 4 adverse event; the most common toxicity was hyperglycemia  
373 (2%).

374 ***Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the***  
375 ***Relapsed Multiple Myeloma Study***

376 Serious adverse events are defined as any event, regardless of causality, that results in death, is  
377 life-threatening, requires hospitalization or prolongs a current hospitalization, results in a  
378 significant disability, or is deemed to be an important medical event. A total of 144 (44%)  
379 patients from the VELCADE treatment arm experienced an SAE during the study, as did 144  
380 (43%) dexamethasone-treated patients. The most commonly reported SAEs in the VELCADE  
381 treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting  
382 (3%). In the dexamethasone treatment group, the most commonly reported SAEs were  
383 pneumonia (7%), pyrexia (4%), and hyperglycemia (3%).

384 A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment group  
385 and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from  
386 treatment due to adverse events assessed as drug-related by the investigators. Among the  
387 331 VELCADE treated patients, the most commonly reported drug-related event leading to  
388 discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone  
389 group, the most commonly reported drug-related events leading to treatment discontinuation  
390 were psychotic disorder and hyperglycemia (2% each).

391 Four deaths were considered to be VELCADE related in this relapsed multiple myeloma study: 1  
392 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac  
393 arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of  
394 bacterial meningitis, and 1 case of sudden death at home.

395 ***Most Commonly Reported Adverse Events in the Relapsed Multiple Myeloma Study***

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

398  
399

**Table 7: Most Commonly Reported Adverse Events (≥10% in VELCADE arm),with Grades 3 and 4 Intensity in the Relapsed 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
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	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

400

401

402 ***Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple***  
403 ***Myeloma***

404 In the phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities  
405 were observed with prolonged VELCADE treatment. These patients were treated for a total of  
406 5.3 to 23 months, including time on VELCADE in the prior VELCADE study. [see *Clinical*  
407 *Studies (14)*]

408 ***Integrated Summary of Safety (Relapsed Multiple Myeloma and Mantle Cell Lymphoma)***

409 Safety data from phase 2 and 3 studies of single agent VELCADE 1.3 mg/m<sup>2</sup>/dose twice weekly  
410 for 2 weeks followed by a 10-day rest period in 1163 patients with previously treated multiple  
411 myeloma (N=1008) and previously treated mantle cell lymphoma (N=155) were integrated and  
412 tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple  
413 myeloma and mantle cell lymphoma. [see *Clinical Studies (14)*]

414 In the integrated analysis, the most commonly reported adverse events were asthenic conditions  
415 (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation  
416 (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral  
417 neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia)  
418 (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty percent (20%) of  
419 patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia  
420 (5%) and neutropenia (3%).

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

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

426 Adverse events thought by the investigator to be drug-related and leading to discontinuation  
427 occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy  
428 (8%), asthenic conditions (3%) and thrombocytopenia and diarrhea (each 2%).

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

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

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

437  
438  
439

**Table 8: Most Commonly Reported (≥10% Overall) Adverse Events in Integrated Analyses of Relapsed 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	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

440

441 **Description of Selected Adverse Events from the Phase 2 and 3 Relapsed Multiple Myeloma**  
442 **and Phase 2 Mantle Cell Lymphoma Studies**

443 ***Gastrointestinal Events***

444 A total of 87% of patients experienced at least one GI disorder. The most common GI disorders  
445 included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders  
446 included dyspepsia and dysgeusia. Grade 3 GI events occurred in 18% of patients; Grade 4  
447 events were 1%. GI events were considered serious in 11% of patients. Five percent (5%) of  
448 patients discontinued due to a GI event. Nausea was reported more often in patients with  
449 multiple myeloma (57%) compared to patients with mantle cell lymphoma (44%). [*see*  
450 ***Warnings and Precautions (5.7)***]

451 ***Thrombocytopenia***

452 Across the studies, VELCADE associated thrombocytopenia was characterized by a decrease in  
453 platelet count during the dosing period (days 1 to 11) and a return toward baseline during the 10-  
454 day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 36% of  
455 patients. Thrombocytopenia was Grade 3 in 24%,  $\geq$ Grade 4 in 5%, and serious in 3% of  
456 patients, and the event resulted in VELCADE discontinuation in 2% of patients [*see Warnings*  
457 ***and Precautions (5.8)***]. Thrombocytopenia was reported more often in patients with multiple  
458 myeloma (38%) compared to patients with mantle cell lymphoma (21%). The incidence of  
459  $\geq$ Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (32%) compared  
460 to patients with mantle cell lymphoma (11%). [*see Warnings and Precautions (5.8)*]

461 ***Peripheral Neuropathy***

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

467 In the relapsed multiple myeloma study, among the 87 patients who experienced  $\geq$  Grade 2  
468 peripheral neuropathy, 51% had improved or resolved with a median of 3.5 months from first  
469 onset.

470 Among the patients with peripheral neuropathy in the phase 2 multiple myeloma studies that was  
471 Grade 2 and led to discontinuation or was  $\geq$ Grade 3, 73% (24 of 33) reported improvement or  
472 resolution following VELCADE dose adjustment, with a median time to improvement of one  
473 Grade or more from the last dose of VELCADE of 33 days. [*see Warnings and Precautions*  
474 ***(5.2)***]

475 ***Hypotension***

476 The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension  
477 NOS) was 13% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the  
478 majority of patients and Grade 3 in 3% and  $\geq$ Grade 4 in <1%. Three percent (3%) of patients  
479 had hypotension reported as an SAE, and 1% discontinued due to hypotension. The incidence of  
480 hypotension was similar in patients with multiple myeloma (12%) and those with mantle cell  
481 lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal  
482 event. Doses of antihypertensive medications may need to be adjusted in patients receiving  
483 VELCADE. [*see Warnings and Precautions (5.3)*]

484 ***Neutropenia***

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

488 Neutropenia was reported as a serious event in  $<1\%$  of patients and  $<1\%$  of patients discontinued  
489 due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma  
490 (18%) compared to patients with mantle cell lymphoma (6%). The incidence of  $\geq$ Grade 3  
491 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with  
492 mantle cell lymphoma (4%). [*see Warnings and Precautions (5.8)*]

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

494 Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and  
495  $\geq$ Grade 4 in  $<1\%$  of patients. Four percent (4%) of patients discontinued treatment due to  
496 asthenia. Asthenic conditions were reported in 62% of patients with multiple myeloma and 72%  
497 of patients with mantle cell lymphoma.

498 ***Pyrexia***

499 Pyrexia ( $>38^{\circ}\text{C}$ ) was reported as an adverse event for 34% of patients. The event was Grade 3 in  
500 3% and  $\geq$ Grade 4 in  $<1\%$ . Pyrexia was reported as a serious adverse event in 6% of patients and  
501 led to VELCADE discontinuation in  $<1\%$  of patients. The incidence of pyrexia was higher  
502 among patients with multiple myeloma (37%) compared to patients with mantle cell lymphoma  
503 (19%). The incidence of  $\geq$ Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in  
504 patients with mantle cell lymphoma.

505 ***Herpes Virus Infection***

506 Physicians should consider using antiviral prophylaxis in subjects being treated with VELCADE.  
507 In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster  
508 reactivation was more common in subjects treated with VELCADE (13%) than in the control  
509 groups (4-5%). Herpes simplex was seen in 2-8% in subjects treated with VELCADE and 1-5%  
510 in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus  
511 reactivation in the VELCADE, melphalan and prednisone arm was less common in subjects  
512 receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic  
513 antiviral therapy (17%). In the postmarketing experience, rare cases of herpes  
514 meningoencephalitis and ophthalmic herpes have been reported.

515 ***Additional Adverse Events from Clinical Studies***

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

520 ***Blood and lymphatic system disorders:*** Disseminated intravascular coagulation, lymphopenia,  
521 leukopenia

522 ***Cardiac disorders:*** Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia,  
523 sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia,  
524 myocardial infarction, pericarditis, pericardial effusion, Torsades de pointes, ventricular  
525 tachycardia

526

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

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

529 **Gastrointestinal disorders:** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis  
530 hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction,  
531 paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal  
532 perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal  
533 reflux

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

536 **Hepatobiliary disorders:** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein  
537 thrombosis, hepatitis, liver failure

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

540 **Infections and infestations:** Aspergillosis, bacteremia, urinary tract infection, herpes viral  
541 infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related  
542 infection

543 **Injury, poisoning and procedural complications:** Catheter related complication, skeletal  
544 fracture, subdural hematoma

545 **Metabolism and nutrition disorders:** Hypocalcemia, hyperuricemia, hypokalemia,  
546 hyperkalemia, hyponatremia, hypernatremia

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

551 **Psychiatric disorders:** Agitation, confusion, mental status change, psychotic disorder, suicidal  
552 ideation

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

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

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

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

## 564 **6.2 Postmarketing Experience**

565 The following adverse drug reactions have been identified from the worldwide post-marketing  
566 experience with VELCADE. Because these reactions are reported voluntarily from a population  
567 of uncertain size, it is not always possible to reliably estimate their frequency or establish a

568 causal relationship to drug exposure: atrioventricular block complete, cardiac tamponade,  
569 ischemic colitis, encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular  
570 coagulation, hepatitis, acute pancreatitis, acute diffuse infiltrative pulmonary disease, toxic  
571 epidermal necrolysis, herpes meningoencephalitis and ophthalmic herpes.

## 572 **7 DRUG INTERACTIONS**

573 **7.1 Ketoconazole:** Co-administration of ketoconazole, a potent CYP3A inhibitor, increased the  
574 exposure of bortezomib. [*see Pharmacokinetics (12.3)*] Therefore, patients should be closely  
575 monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g.  
576 ketoconazole, ritonavir). [*see Pharmacokinetics (12.3)*]

577 **7.2 Melphalan-Prednisone:** Co-administration of melphalan-prednisone increased the exposure  
578 of bortezomib. However, this increase is unlikely to be clinically relevant. [*see*  
579 *Pharmacokinetics (12.3)*]

580 **7.3 Omeprazole:** Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no  
581 effect on the exposure of bortezomib. [*see Pharmacokinetics (12.3)*]

582 **7.4 Cytochrome P450:** Patients who are concomitantly receiving VELCADE and drugs that are  
583 inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities  
584 or reduced efficacy. [*see Pharmacokinetics (12.3)*]

## 585 **8 USE IN SPECIFIC POPULATIONS**

### 586 **8.1 Pregnancy**

587 Pregnancy Category D [*see Warnings and Precautions (5.1)*]

588 Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits  
589 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  
590 rabbit) when administered during organogenesis. These dosages are approximately half the  
591 clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area.

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

596 There are no adequate and well-controlled studies in pregnant women. If VELCADE is used  
597 during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should  
598 be apprised of the potential hazard to the fetus.

### 599 **8.3 Nursing Mothers**

600 It is not known whether bortezomib is excreted in human milk. Because many drugs are  
601 excreted in human milk and because of the potential for serious adverse reactions in nursing  
602 infants from VELCADE, a decision should be made whether to discontinue nursing or to  
603 discontinue the drug, taking into account the importance of the drug to the mother.

### 604 **8.4 Pediatric Use**

605 The safety and effectiveness of VELCADE in children have not been established.

606 **8.5 Geriatric Use**

607 Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of  
608 age or older: 125 (38%) on the VELCADE arm and 120 (36%) on the dexamethasone arm.  
609 Median time to progression and median duration of response for patients  $\geq 65$  were longer on  
610 VELCADE compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo,  
611 respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged  $\geq 65$  experienced  
612 response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and  
613 4 events was 64%, 78% and 75% for VELCADE patients  $\leq 50$ , 51-64 and  $\geq 65$  years old,  
614 respectively. [*see Adverse Reactions (6.1); Clinical Studies (14)*]

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

618 **8.6 Patients with Renal Impairment**

619 The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment.  
620 Therefore, dosing adjustments of VELCADE are not necessary for patients with renal  
621 insufficiency. Since dialysis may reduce VELCADE concentrations, the drug should be  
622 administered after the dialysis procedure. For information concerning dosing of melphalan in  
623 patients with renal impairment see manufacturer's prescribing information. [*see Clinical*  
624 *Pharmacology (12.3)*]

625 **8.7 Patients with Hepatic Impairment**

626 The exposure of bortezomib is increased in patients with moderate and severe hepatic  
627 impairment. Starting dose should be reduced in those patients. [*see Dosage and Administration*  
628 *(2.5), Warnings and Precautions (5.11), and Pharmacokinetics (12.3)*]

629 **8.8 Patients with Diabetes**

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

634 **10 OVERDOSAGE**

635 There is no known specific antidote for VELCADE overdose [*see Warnings and Precautions*  
636 *(5.3) and Dosage and Administration (2.5)*]. In humans, fatal outcomes following the  
637 administration of more than twice the recommended therapeutic dose have been reported, which  
638 were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the  
639 event of an overdose, the patient's vital signs should be monitored and appropriate supportive  
640 care given.

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

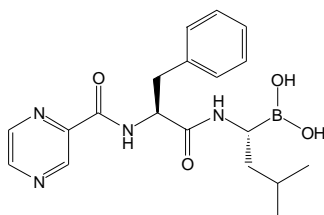
648 **11 DESCRIPTION**

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

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

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

658 Bortezomib has the following chemical structure:



659

660 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  
661 bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to  
662 6.5.

663 **12 CLINICAL PHARMACOLOGY**

664 **12.1 Mechanism of Action**

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

674 **12.2 Pharmacodynamics**

675 Following twice weekly administration of 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> bortezomib doses (n=12 per  
676 each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in  
677 whole blood was observed 5 minutes after drug administration. Comparable maximum  
678 inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m<sup>2</sup> doses. Maximal  
679 inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup> dose  
680 regimens, respectively.

681 **12.3 Pharmacokinetics**

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

685 subsequent doses, when administered twice weekly, the mean maximum observed plasma  
686 concentrations ranged from 67 to 106 ng/mL for the 1 mg/m<sup>2</sup> dose and 89 to 120 ng/mL for the  
687 1.3 mg/m<sup>2</sup> dose. The mean elimination half-life of bortezomib upon multiple dosing ranged  
688 from 40 to 193 hours after the 1 mg/m<sup>2</sup> dose and 76 to 108 hours after the 1.3mg/m<sup>2</sup> dose. The  
689 mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m<sup>2</sup>  
690 and 1.3 mg/m<sup>2</sup>, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses  
691 of 1 and 1.3 mg/m<sup>2</sup>, respectively.

692 **Distribution:** The mean distribution volume of bortezomib ranged from approximately 498 to  
693 1884 L/m<sup>2</sup> following single- or repeat-dose administration of 1 mg/m<sup>2</sup> or 1.3mg/m<sup>2</sup> to patients  
694 with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The  
695 binding of bortezomib to human plasma proteins averaged 83% over the concentration range of  
696 100 to 1000 ng/mL.

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

705 **Elimination:** The pathways of elimination of bortezomib have not been characterized in humans.

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

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

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

714 **Hepatic Impairment:** The effect of hepatic impairment (see **Table 4** for definition of hepatic  
715 impairment) on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at  
716 bortezomib doses ranging from 0.5 to 1.3 mg/m<sup>2</sup>. When compared to patients with normal  
717 hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC.  
718 However, the dose-normalized mean AUC values were increased by approximately 60% in  
719 patients with moderate or severe hepatic impairment. A lower starting dose is recommended in  
720 patients with moderate or severe hepatic impairment, and those patients should be monitored  
721 closely. [*see Dosage and Administration (2.5), Warning and Precautions (5.11) and Use in*  
722 *Specific Populations (8.7)*]

723 **Renal Impairment:** A pharmacokinetic study was conducted in patients with various degrees of  
724 renal impairment who were classified according to their creatinine clearance values (CrCl) into  
725 the following groups: Normal (CrCl ≥60 mL/min/1.73 m<sup>2</sup>, N=12), Mild (CrCl=40-59  
726 mL/min/1.73 m<sup>2</sup>, N=10), Moderate (CrCl=20-39 mL/min/1.73 m<sup>2</sup>, N=9), and Severe (CrCl < 20  
727 mL/min/1.73 m<sup>2</sup>, N=3). A group of dialysis patients who were dosed after dialysis was also  
728 included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m<sup>2</sup>

729 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and  $C_{max}$ ) was  
730 comparable among all the groups. [see *Use in Specific Populations (8.6)*]

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

732 **Effect of Ketoconazole:** Co-administration of ketoconazole, a potent CYP3A inhibitor, showed a  
733 35% increase in mean bortezomib AUC, based on data from 12 patients. [see *Drug Interactions*  
734 *(7.1)*]

735 **Effect of Melphalan-Prednisone:** Co-administration of melphalan-prednisone on VELCADE  
736 showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This increase  
737 is unlikely to be clinically relevant. [see *Drug Interactions (7.2)*]

738 **Effect of Omeprazole:** Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no  
739 significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients. [see  
740 *Drug Interactions (7.3)*]

741 **Cytochrome P450:** Bortezomib is a poor inhibitor of human liver microsome cytochrome P450  
742 1A2, 2C9, 2D6, and 3A4, with  $IC_{50}$  values of  $>30\mu M$  ( $>11.5\mu g/mL$ ). Bortezomib may inhibit  
743 2C19 activity ( $IC_{50} = 18\mu M$ ,  $6.9\mu g/mL$ ) and increase exposure to drugs that are substrates for  
744 this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in  
745 primary cultured human hepatocytes. [see *Drug Interactions (7.4)*]

## 746 **13 NONCLINICAL TOXICOLOGY**

### 747 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

748 Carcinogenicity studies have not been conducted with bortezomib.

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

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

### 758 **13.2 Animal Toxicology**

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

766 **Chronic Administration:** In animal studies at a dose and schedule similar to that recommended  
767 for patients (twice weekly dosing for 2 weeks followed by 1-week rest), toxicities observed  
768 included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid  
769 system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling

770 and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord.  
771 Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

## 772 **14 CLINICAL STUDIES**

### 773 **14.1 Multiple Myeloma**

#### 774 **Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple** 775 **Myeloma:**

776 A prospective, international, randomized (1:1), open-label clinical study of 682 patients was  
777 conducted to determine whether VELCADE (1.3 mg/m<sup>2</sup>) in combination with melphalan  
778 (9 mg/m<sup>2</sup>) and prednisone (60 mg/m<sup>2</sup>) resulted in improvement in time to progression (TTP)  
779 when compared to melphalan (9 mg/m<sup>2</sup>) and prednisone (60 mg/m<sup>2</sup>) in patients with previously  
780 untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles  
781 (approximately 54 weeks) and was discontinued early for disease progression or unacceptable  
782 toxicity. Antiviral prophylaxis was recommended for patients on the VELCADE study arm.

783 The median age of the patients in the study was 71 years (48;91), 50% were male, 88% were  
784 Caucasian and the median Karnofsky performance status score for the patients was 80 (60;100).  
785 Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of  
786 105 g/L (64;165), and a median platelet count of 221,500 /microliter (33,000;587,000).

787 Efficacy results for the trial are presented in Table 9. At a pre-specified interim analysis (with  
788 median follow-up of 16.3 months), the combination of VELCADE, Melphalan and Prednisone  
789 therapy resulted in significantly superior results for time to progression, progression free  
790 survival, overall survival and response rate. Further enrollment was halted, and patients receiving  
791 Melphalan and Prednisone were offered VELCADE in addition. A later, pre-specified analysis  
792 of overall survival (with median follow-up of 36.7 months) continued to show a statistically  
793 significant survival benefit for the VELCADE, Melphalan and Prednisone treatment arm despite  
794 subsequent therapies including VELCADE based regimens.

795

796  
797

**Table 9: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study**

<b>Efficacy Endpoint</b>	<b>VELCADE, Melphalan and Prednisone n=344</b>	<b>Melphalan and Prednisone n=338</b>
<b>Time to Progression</b>		
Events n (%)	101 (29)	152 (45)
Median <sup>a</sup> (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio <sup>b</sup>	0.54	
(95% CI)	(0.42, 0.70)	
p-value <sup>c</sup>	0.000002	
<b>Progression-free Survival</b>		
Events n (%)	135 (39)	190 (56)
Median <sup>a</sup> (months)	18.3	14.0
(95% CI)	(16.6, 21.7)	(11.1, 15.0)
Hazard ratio <sup>b</sup>	0.61	
(95% CI)	(0.49, 0.76)	
p-value <sup>c</sup>	0.00001	
<b>Response Rate</b>		
CR <sup>d</sup> n (%)	102 (30)	12 (4)
PR <sup>d</sup> n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR <sup>d</sup> n (%)	238 (69)	115 (34)
p-value <sup>e</sup>	<10 <sup>-10</sup>	
<b>Overall Survival</b>		
Events (deaths) n (%)	109 (32)	148 (44)
Median <sup>a</sup> (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio <sup>b</sup>	0.65	
(95% CI)	(0.51, 0.84)	
p-value <sup>c</sup>	0.00084	

798 Note: All results are based on the analysis performed at a median follow-up duration of 16.3  
799 months except for the overall survival analysis that was performed at a median follow-up  
800 duration of 36.7 months.

801 <sup>a</sup> Kaplan-Meier estimate

802 <sup>b</sup> Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification  
803 factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an  
804 advantage for VELCADE, Melphalan and Prednisone

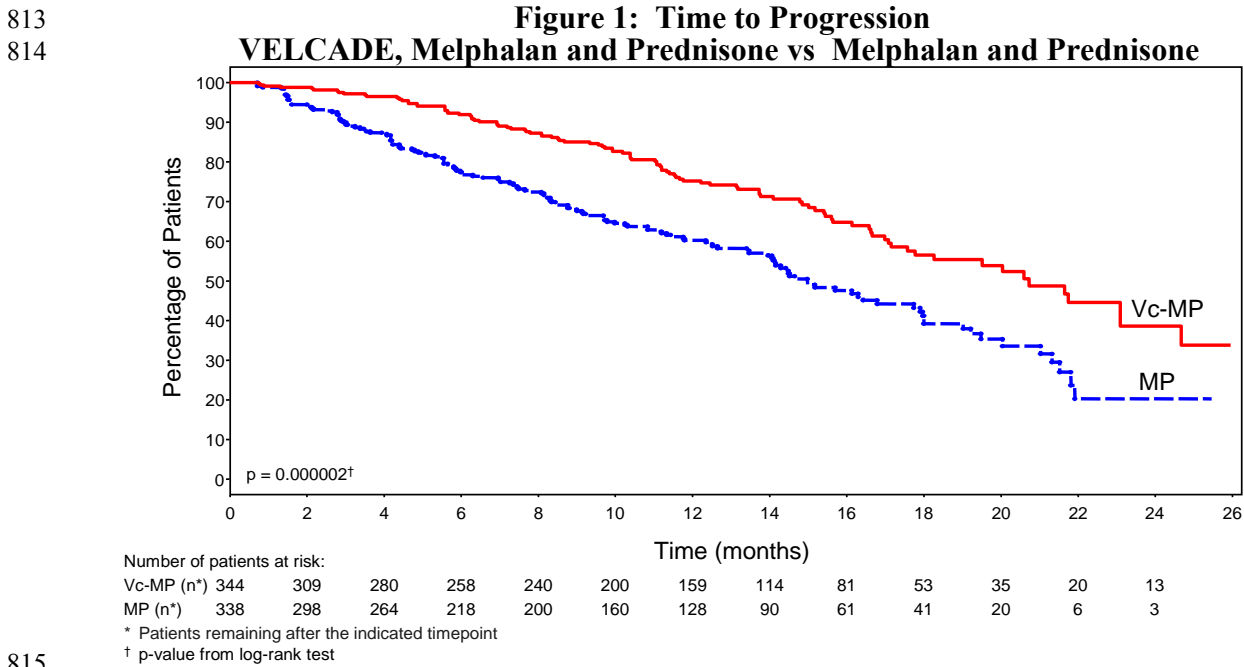
805 <sup>c</sup> p-value based on the stratified log-rank test adjusted for stratification factors: beta2-  
806 microglobulin, albumin, and region

807 <sup>d</sup> EBMT criteria

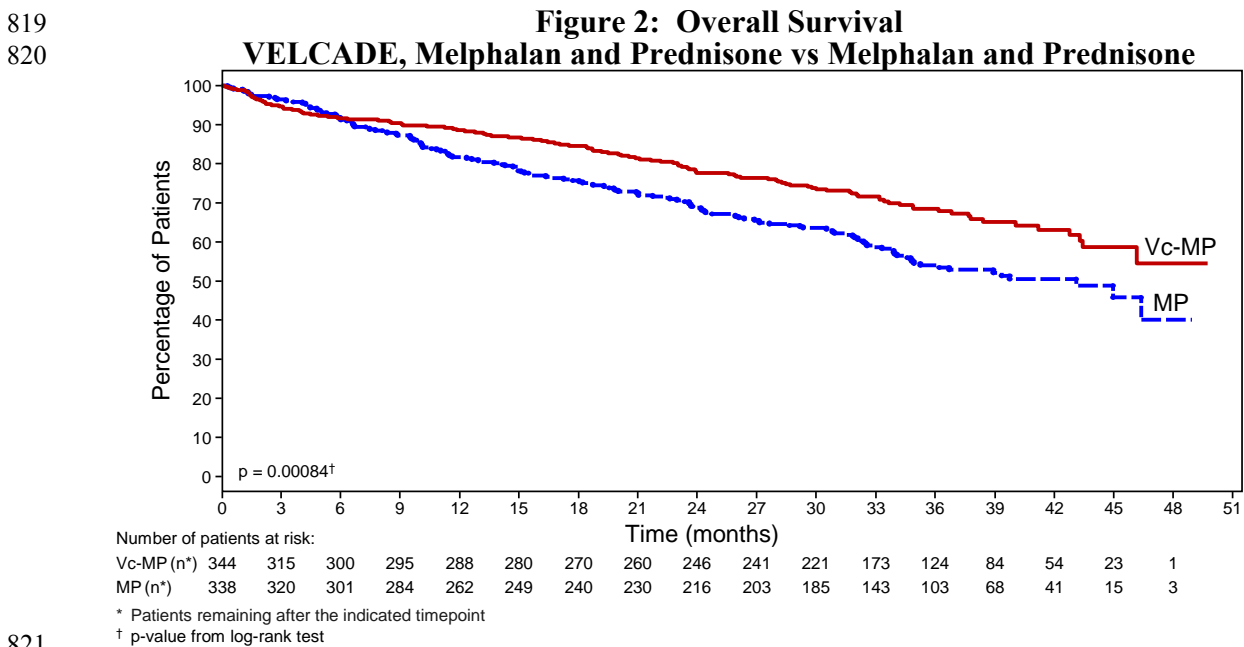
808 <sup>e</sup> p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test  
809 adjusted for the stratification factors

810

811 TTP was statistically significantly longer on the VELCADE, Melphalan and Prednisone arm (see  
 812 **Figure 1**). (median follow up 16.3 months)



815  
 816  
 817 Overall survival was statistically significantly longer on the VELCADE, Melphalan and  
 818 Prednisone arm (see Figure 2). (median follow up 36.7 months)



821  
 822  
 823 **Randomized, Clinical Study in Relapsed Multiple Myeloma**  
 824 A prospective phase 3, international, randomized (1:1), stratified, open-label clinical study  
 825 enrolling 669 patients was designed to determine whether VELCADE resulted in improvement

826 in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive  
 827 multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior  
 828 high-dose dexamethasone were excluded as were those with baseline grade  $\geq 2$  peripheral  
 829 neuropathy or platelet counts  $< 50,000/\mu\text{L}$ . A total of 627 patients were evaluable for response.

830 Stratification factors were based on the number of lines of prior therapy the patient had  
 831 previously received (1 previous line versus more than 1 line of therapy), time of progression  
 832 relative to prior treatment (progression during or within 6 months of stopping their most recent  
 833 therapy versus relapse  $> 6$  months after receiving their most recent therapy), and screening  
 834  $\beta_2$ -microglobulin levels ( $\leq 2.5$  mg/L versus  $> 2.5$  mg/L).

835 Baseline patient and disease characteristics are summarized in **Table 10**.

836 **Table 10: Summary of Baseline Patient and Disease Characteristics**  
 837 **in the Relapsed 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 $< 75 \times 10^9/\text{L}$	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%

838 Patients in the VELCADE treatment group were to receive eight 3-week treatment cycles  
 839 followed by three 5-week treatment cycles of VELCADE. Patients achieving a CR were treated  
 840 for 4 cycles beyond first evidence of CR. Within each 3-week treatment cycle, VELCADE  
 841  $1.3 \text{ mg}/\text{m}^2/\text{dose}$  alone was administered by IV bolus twice weekly for 2 weeks on Days 1, 4, 8,  
 842 and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment cycle,

843 VELCADE 1.3 mg/m<sup>2</sup>/dose alone was administered by IV bolus once weekly for 4 weeks on  
844 Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35). [*see Dosage and*  
845 *Administration(2.1)*]

846 Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles  
847 followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone  
848 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a  
849 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone  
850 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period  
851 (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered  
852 VELCADE at a standard dose and schedule on a companion study. Following a preplanned  
853 interim analysis of time to progression, the dexamethasone arm was halted and all patients  
854 randomized to dexamethasone were offered VELCADE, regardless of disease status.

855 In the VELCADE arm, 34% of patients received at least one VELCADE dose in all 8 of the  
856 3-week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average  
857 number of VELCADE doses during the study was 22, with a range of 1 to 44. In the  
858 dexamethasone arm, 40% of patients received at least one dose in all 4 of the 5-week treatment  
859 cycles of therapy, and 6% received at least one dose in all 9 cycles.

860 The time to event analyses and response rates from the relapsed multiple myeloma study are  
861 presented in **Table 11**. Response and progression were assessed using the European Group for  
862 Blood and Marrow Transplantation (EBMT) criteria.<sup>1</sup> Complete response (CR) required <5%  
863 plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test  
864 (IF). Partial response (PR) requires ≥50% reduction in serum myeloma protein and ≥90%  
865 reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks  
866 along with stable bone disease and normal calcium. Near complete response (nCR) was defined  
867 as meeting all the criteria for complete response including 100% reduction in M-protein by  
868 protein electrophoresis, however M-protein was still detectable by immunofixation (IF<sup>+</sup>).

**Table 11: Summary of Efficacy Analyses in the Relapsed 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	

870 <sup>a</sup> Kaplan-Meier estimate871 <sup>b</sup> Hazard ratio is based on Cox proportional-hazard model with the treatment as single  
872 independent variable. A hazard ratio less than 1 indicates an advantage for VELCADE873 <sup>c</sup> p-value based on the stratified log-rank test including randomization stratification factors874 <sup>d</sup> Precise p-value cannot be rendered875 <sup>e</sup> Response population includes patients who had measurable disease at baseline and received at  
876 least 1 dose of study drug877 <sup>f</sup> EBMT criteria<sup>1</sup>; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT  
878 criteria nCR is in the PR category879 <sup>g</sup> In 2 patients, the IF was unknown880 <sup>h</sup> p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test  
881 adjusted for the stratification factors

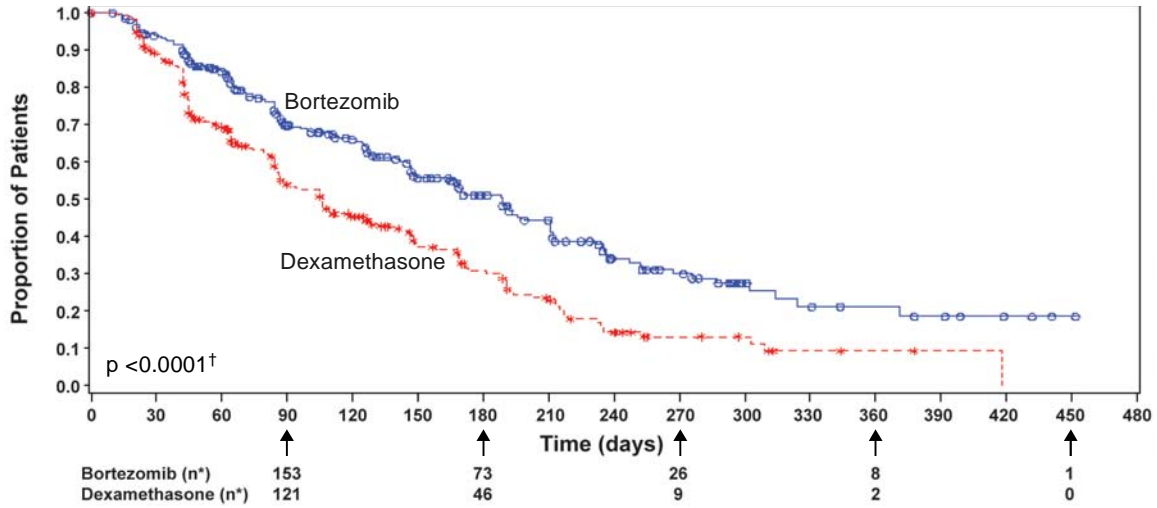
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883 TTP was statistically significantly longer on the VELCADE arm (see Figure 3).

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**Figure 3: Time to Progression  
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)**

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

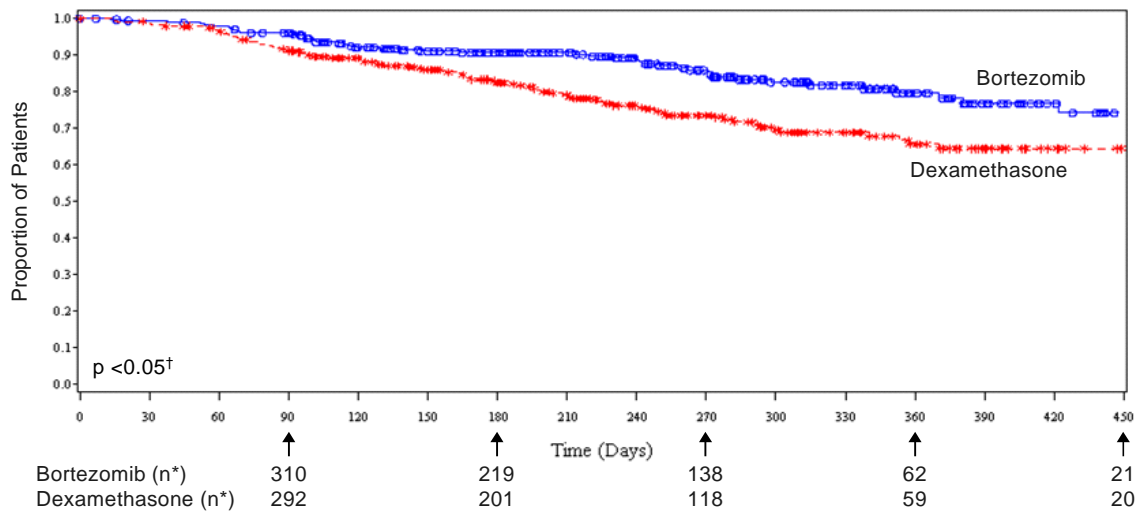
887

888 As shown in **Figure 4** VELCADE had a significant survival advantage relative to  
889 dexamethasone ( $p < 0.05$ ). The median follow-up was 8.3 months.

890

**Figure 4: Overall Survival  
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)**

893



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

894

895 For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median  
896 duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2  
897 months) for the 56 responders on the dexamethasone arm. The response rate was significantly  
898 higher on the VELCADE arm regardless of  $\beta_2$ -microglobulin levels at baseline.

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

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

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

909 Patients from the two phase 2 studies who in the investigators' opinion would experience  
910 additional clinical benefit continued to receive VELCADE beyond 8 cycles on an extension  
911 study. Sixty-three (63) patients from the phase 2 multiple myeloma studies were enrolled and  
912 received a median of 7 additional cycles of VELCADE therapy for a total median of 14 cycles  
913 (range 7 to 32). The overall median dosing intensity was the same in both the parent protocol  
914 and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the  
915 same or higher dose intensity at which they completed the parent protocol, and 89% of patients  
916 maintained the standard 3-week dosing schedule during the extension study. No new cumulative  
917 or new long-term toxicities were observed with prolonged VELCADE treatment. [*see Adverse*  
918 *Reactions(6.1)*]

### 919 **14.2 Mantle Cell Lymphoma**

#### 920 ***A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma After Prior Therapy***

921 The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were  
922 evaluated in an open-label, single-arm, multicenter study of 155 patients with progressive disease  
923 who had received at least 1 prior therapy. The median age of the patients was 65 years (42, 89),  
924 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of  
925 disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the  
926 following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty  
927 seven percent (37%) of patients were refractory to their last prior therapy. An IV bolus injection  
928 of VELCADE 1.3 mg/m<sup>2</sup>/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and  
929 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles.  
930 Patients achieving a CR or CRu were treated for 4 cycles beyond first evidence of CR or CRu.  
931 The study employed dose modifications for toxicity. [*see Dosage and Administration (2.4)*]

932 Responses to VELCADE are shown in Table 12. Response rates to VELCADE were determined  
933 according to the International Workshop Response Criteria (IWRC)<sup>2</sup> based on independent  
934 radiologic review of CT scans. The median number of cycles administered across all patients  
935 was 4; in responding patients the median number of cycles was 8. The median time to response  
936 was 40 days (range 31 to 204 days). The median duration of follow-up was more than 13  
937 months.

**Table 12: 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)

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960 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

963 NDC 63020-049-01  
964 3.5 mg single use vial

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

968 Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic  
969 drugs, including the use of gloves and other protective clothing to prevent skin contact<sup>3-6</sup>.

970

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

972 U.S. Patents: 5,780,454; 6,083,903; 6,297,217 B1; 6,617,317 B1; 6,713, 446 B2; 6,958,319 B2

973 ***Distributed and Marketed by:***  
974 Millennium Pharmaceuticals, Inc.  
975 40 Landsdowne Street  
976 Cambridge, MA 02139

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## 17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following with patients prior to treatment with VELCADE:

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

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

**Pregnancy/Nursing:** Patients should be advised to use effective contraceptive measures to prevent pregnancy during treatment with VELCADE. If a patient becomes pregnant during treatment she should be instructed to inform her physician immediately. Patients should also be advised not to take VELCADE treatment while pregnant or breast-feeding. If a patient wishes to restart breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician.

**Concomitant Medications:** Patients should be advised to speak with their physician about any other medication they are currently taking.

**Diabetic Patients:** Patients should be advised to check their blood sugar frequently if using an oral antidiabetic medication and notify their physician of any changes in blood sugar level.


**Peripheral Neuropathy:** Patients should be advised to contact their physician if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

**Other:** Patients should be instructed to contact their physician if they develop a rash, experience shortness of breath, cough, or swelling of the feet, ankles, or legs, convulsion, persistent headache, reduced eyesight, an increase in blood pressure or blurred vision.

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Cambridge, MA 02139

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