

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 US Approval: 2003**
 8 -----**RECENT MAJOR CHANGES**-----
 9 Warnings and Precautions, Peripheral Neuropathy (5.2);
 10 Pulmonary Disorders (5.5); Neutropenia (5.8) 3/2006
 11 Indications and Usage, Mantle Cell Lymphoma (1.2) 12/2006
 12 Warnings and Precautions, RPLS (5.6) 12/2006
 13 Patients with Renal Impairment (8.6) tbd
 14 -----**INDICATIONS AND USAGE**-----
 15 VELCADE is a proteasome inhibitor indicated for:
 16 • treatment of patients with multiple myeloma who have received at
 17 least 1 prior therapy (1.1)
 18 • treatment of patients with mantle cell lymphoma who have received at
 19 least 1 prior therapy (1.2)
 20 -----**DOSAGE AND ADMINISTRATION**-----
 21 • The recommended dose of VELCADE is 1.3 mg/m² administered as
 22 a bolus intravenous injection twice weekly for 2 weeks (Days 1, 4, 8,
 23 and 11) every 21 days. (2.1)
 24 • For extended therapy of more than 8 cycles, VELCADE may be
 25 administered on the standard schedule or once weekly for 4 weeks
 26 (Days 1, 8, 15 and 22) every 35 days. (2.1)
 27 • VELCADE therapy should be withheld at the onset of any Grade 3
 28 non-hematological or Grade 4 hematological toxicities. Once the
 29 symptoms of the toxicity have resolved, VELCADE therapy may be
 30 reinitiated at a 25% reduced dose (1.3 mg/m² /dose reduced to 1
 31 mg/m²/dose, 1 mg/m²/dose reduced to 0.7 mg/m²/dose). (2.2, 5.2)
 32 • Manage peripheral neuropathy with dose modification. (2.2)
 33 -----**DOSAGE FORMS AND STRENGTHS**-----
 34 • 1 vial contains 3.5 mg of bortezomib. Dose must be individualized to
 35 prevent overdose. (3)
 36 -----**CONTRAINDICATIONS**-----
 37 • VELCADE is contraindicated in patients with hypersensitivity to
 38 bortezomib, boron, or mannitol. (4)

40 -----**WARNINGS AND PRECAUTIONS**-----
 41 • Women should avoid becoming pregnant while being treated with
 42 VELCADE. Pregnant women should be apprised of the potential
 43 harm to the fetus. (5.1)
 44 • Peripheral neuropathy, including severe cases, may occur - manage
 45 with dose modification or discontinuation. (2.2) Patients with
 46 preexisting severe neuropathy should be treated with VELCADE
 47 after careful risk-benefit assessment. (2.2, 5.2)
 48 • Hypotension can occur. Caution should be used when treating
 49 patients receiving antihypertensives, those with a history of
 50 syncope, and those who are dehydrated. (5.3)
 51 • Patients with risk factors for, or existing heart disease, should be
 52 closely monitored. (5.4)
 53 • Acute diffuse infiltrative pulmonary disease has been reported.
 54 (5.5)
 55 • Nausea, diarrhea, constipation, and vomiting have occurred and
 56 may require use of antiemetic and antidiarrheal medications or
 57 fluid replacement. (5.7)
 58 • Thrombocytopenia or neutropenia can occur; complete blood
 59 counts should be regularly monitored throughout treatment. (5.8)
 60 • Tumor Lysis Syndrome (5.9), Reversible Posterior
 61 Leukoencephalopathy Syndrome (5.6), and acute hepatic failure
 62 (5.10) have been reported.
 63 -----**ADVERSE REACTIONS**-----
 64 Most common adverse reactions (incidence ≥30%) include asthenic
 65 conditions, diarrhea, nausea, constipation, peripheral neuropathy,
 66 vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia
 67 and decreased appetite. Other adverse reactions, including serious
 68 adverse reactions, have been reported. (6.1)
 69 **To report SUSPECTED ADVERSE REACTIONS, contact**
 70 **Millennium Pharmaceuticals at (1-866 VELCADE or**
 71 **www.mlmm.com) or FDA at 1-800-FDA-1088 or**
 72 **www.fda.gov/medwatch.**
 73 -----**USE IN SPECIFIC POPULATIONS**-----
 74 • Women should be advised against breast feeding or becoming
 75 pregnant while being treated with VELCADE. (5.1, 8.3)
 76 • Dosing adjustments are not necessary for patients with renal
 77 insufficiency, including those requiring dialysis. (8.6)
 78 • No overall differences in safety or effectiveness were observed
 79 between patients ≥ age 65 and younger patients receiving
 80 VELCADE; but greater sensitivity of some older individuals
 81 cannot be ruled out. (8.5)
 82 • Patients with diabetes may require close monitoring of blood
 83 glucose and adjustment of antidiabetic medication. (8.8)
 84 **See 17 for PATIENT COUNSELING INFORMATION.**
 85 **Revised: [3/2007]**

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138 FULL PRESCRIBING INFORMATION

139 1 INDICATIONS AND USAGE

140 1.1 Multiple Myeloma

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

143 1.2 Mantle Cell Lymphoma

144 VELCADE[®] (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who
145 have received at least 1 prior therapy.

146 2 DOSAGE AND ADMINISTRATION

147 2.1 Dosage

148 The recommended dose of VELCADE is 1.3 mg/m²/dose administered as a 3 to 5 second bolus intravenous
149 injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For
150 extended therapy of more than 8 cycles, VELCADE may be administered on the standard schedule or on a
151 maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23
152 to 35). [*see Clinical Studies section (14) for a description of dose administration during the trials*] At least 72
153 hours should elapse between consecutive doses of VELCADE.

154 2.2 Dose Modification and Re-initiation of Therapy

155 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological
156 toxicities excluding neuropathy as discussed below [*see Warnings and Precautions (5)*]. Once the symptoms of the
157 toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1
158 mg/m²/dose; 1 mg/m²/dose reduced to 0.7 mg/m²/dose).

159 **Table 1** contains the recommended dose modifications for the management of patients who experience VELCADE
160 related neuropathic pain and/or peripheral neuropathy. Patients with preexisting severe neuropathy should be treated
161 with VELCADE only after careful risk-benefit assessment.

162
163**Table 1: 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 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinstate with a reduced dose of VELCADE at 0.7 mg/m ² and change treatment schedule to once per week.
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE

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

165 2.3 Administration Precautions166 The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in
167 calculating the dose to prevent overdose.168 VELCADE is an antineoplastic. Procedures for proper handling and disposal should be considered. See How
169 Supplied/Storage and Handling for specific recommendations and guidelines.170 In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not
171 associated with tissue damage.**172 2.4 Reconstitution/Preparation for Intravenous Administration**173 Proper aseptic technique should be used. Reconstitute with 3.5 mL of 0.9% Sodium Chloride resulting in a final
174 concentration of 1 mg/mL of bortezomib. The reconstituted product should be a clear and colorless solution.175 Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration
176 whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted
177 product should not be used.178 **Stability:** Unopened vials of VELCADE are stable until the date indicated on the package when stored in the
179 original package protected from light.180 VELCADE contains no antimicrobial preservative. Reconstituted VELCADE should be administered within 8
181 hours of preparation. When reconstituted as directed, VELCADE may be stored at 25°C (77°F). The reconstituted
182 material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for
183 up to 8 hours in a syringe; however total storage time for the reconstituted material must not exceed 8 hours when
184 exposed to normal indoor lighting.**185 3 DOSAGE FORMS AND STRENGTHS**

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

187 4 CONTRAINDICATIONS

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

189 5 WARNINGS AND PRECAUTIONS190 VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic
191 therapy. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE.**192 5.1 Pregnancy Category D**

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

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

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

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

204 **5.2 Peripheral Neuropathy**

205 VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe
206 sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain
207 or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral
208 neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of
209 neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or
210 weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and
211 schedule of VELCADE [see *Dosage and Administration (2.2)*]. Following dose adjustments, improvement in or
212 resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral neuropathy in the
213 phase 3 multiple myeloma study. Improvement in or resolution of peripheral neuropathy was reported in 73% of
214 patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2
215 multiple myeloma studies. [see *Adverse Reactions (6.1)*] The long-term outcome of peripheral neuropathy has not
216 been studied in mantle cell lymphoma.

217 **5.3 Hypotension**

218 The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%. These events are observed
219 throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving
220 medications known to be associated with hypotension, and patients who are dehydrated. Management of
221 orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and
222 administration of mineralocorticoids and/or sympathomimetics. [see *Adverse Reactions(6.1)*]

223 **5.4 Cardiac Disorders**

224 Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection
225 fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection
226 fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the phase 3 multiple
227 myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and
228 dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure,
229 congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone
230 groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies;
231 causality has not been established.

232 **5.5 Pulmonary Disorders**

233 There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as
234 pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients
235 receiving VELCADE. Some of these events have been fatal. A higher proportion of these events have been
236 reported in Japan.

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

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

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

244 5.6 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

245 There have been rare reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible, neurological
246 disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual
247 and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm
248 the diagnosis. In patients developing RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy
249 in patients previously experiencing RPLS is not known.

250 5.7 Gastrointestinal Adverse Events

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

254 5.8 Thrombocytopenia/Neutropenia

255 VELCADE is associated with thrombocytopenia and neutropenia. Platelets and neutrophils were lowest at Day 11 of
256 each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. The cyclical pattern of
257 platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and
258 there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was
259 approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in
260 **Table 2**. In the phase 3 multiple myeloma study, the incidence of significant bleeding events (\geq Grade 3) was
261 similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to
262 each dose of VELCADE. VELCADE therapy should be held when the platelet count is $<25,000/\mu\text{L}$ and reinitiated
263 at a reduced dose [*see Dosage and Administration (2.2); Adverse Reactions (6)*]. There have been reports of
264 gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may be considered. The
265 incidence of febrile neutropenia was $<1\%$.

266 **Table 2: Severity of Thrombocytopenia Related to Pretreatment**
267 **Platelet Count in the Phase 3 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%)

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

269 ** Data were missing at baseline for 1 patient

270 5.9 Tumor Lysis Syndrome

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

274 5.10 Hepatic Events

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

279 **Patients with Hepatic Impairment:** Bortezomib is metabolized by liver enzymes and bortezomib's clearance may
280 decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated
281 with VELCADE. [*see Drug Interactions (7); Use In Specific Populations (8.7)*]

282 5.11 Drug / Laboratory Test Interactions

283 None known.

284 **6 ADVERSE REACTIONS**

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

- 286 • Peripheral Neuropathy [*see Warnings and Precautions (5.2); Dosage and Administration (2.2)*]
- 287 • Hypotension [*see Warnings and Precautions (5.3)*]
- 288 • Cardiac Disorders [*see Warnings and Precautions (5.4)*]
- 289 • Pulmonary Disorders [*see Warnings and Precautions (5.5)*]
- 290 • Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and Precautions (5.6)*]
- 291 • Gastrointestinal Adverse Events [*see Warnings and Precautions (5.7)*]
- 292 • Thrombocytopenia/Neutropenia [*see Warnings and Precautions (5.8)*]
- 293 • Tumor Lysis Syndrome [*see Warnings and Precautions (5.9)*]
- 294 • Hepatic Events [*see Warnings and Precautions (5.10)*]

295 **6.1 Clinical Trials Experience**

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

299 ***Randomized Open-Label Phase 3 Multiple Myeloma Study***

300 The safety data described below and in Table 3 reflect exposure to either VELCADE (n=331) or dexamethasone
301 (n=332) in a study of patients with multiple myeloma. VELCADE was administered intravenously at doses of 1.3
302 mg/m² twice weekly for 2 out of 3 weeks (21 day cycle). After eight 21-day cycles patients continued therapy for
303 three 35-day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (9 months) with a median
304 duration of 6 cycles (4.1 months). For inclusion in the trial patients must have had measurable disease and 1 to 3
305 prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and
306 bilirubin levels as high as 1.5 times the upper limit of normal. The overall frequency of adverse events was similar
307 in men and women, and in patients <65 and ≥above and below 65 years of age. Most patients were Caucasian. [*see*
308 *Clinical Studies (14.1)*]

309 Among the 331 VELCADE treated patients, the most commonly reported events overall were asthenic conditions
310 (61%), diarrhea and nausea (each 57%), constipation (42%), peripheral neuropathy NEC (36%), vomiting, pyrexia,
311 thrombocytopenia, and psychiatric disorders (each 35%), anorexia and appetite decreased (34%), paresthesia and
312 dysesthesia (27%), anemia and headache (each 26%), and cough (21%). The most commonly reported adverse
313 events reported among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic
314 conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung infections (each 21%).
315 Fourteen percent (14%) of patients in the VELCADE treated arm experienced a Grade 4 adverse event; the most
316 common toxicities were thrombocytopenia (4%), neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%)
317 of dexamethasone treated patients experienced a Grade 4 adverse event; the most common toxicity was
318 hyperglycemia (2%).

319 ***Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Phase 3 Multiple Myeloma Study.***

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

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

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

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

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

341
342**Table 3: 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
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy ^a	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	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

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

346 **Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma**
347 In the phase 2 extension study of 63 patients no new cumulative or new long-term toxicities were observed with
348 prolonged VELCADE treatment. These patients were treated for a total of 5.3 to 23 months, including time on
349 VELCADE in the prior VELCADE study. [see *Clinical Studies (14)*]

350 **Integrated Summary of Safety (Multiple Myeloma and Mantle Cell Lymphoma)**
351 Safety data from phase 2 and 3 studies of VELCADE 1.3 mg/m²/dose twice weekly for 2 weeks followed by a 10-
352 day rest period in 1163 patients with previously treated multiple myeloma (N=1008) and previously treated mantle
353 cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar
354 in patients with multiple myeloma and mantle cell lymphoma. [see *Clinical Studies (14)*]

355 In the integrated analysis, the most commonly reported adverse events were asthenic conditions (including fatigue,
356 malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy NEC
357 (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and
358 appetite decreased (including anorexia) (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty
359 percent (20%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia
360 (5%) and neutropenia (3%).

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

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

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

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

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

373 The most common adverse events are shown in **Table 4**. All adverse events occurring at ≥10% are included. In the
374 absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are
375 drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse
376 reactions that follows.

377
378
379

**Table 4: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events
in Integrated Analyses of Multiple Myeloma and Mantle Cell Lymphoma Studies
using the 1.3 mg/m² Dose (N=1163)**

Adverse Events	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
	All Events	\geq Grade 3	All Events	\geq Grade 3	All Events	\geq 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 ^a	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

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

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

385 **Gastrointestinal Events:**

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

392 **Thrombocytopenia**

393 Across the studies, VELCADE associated thrombocytopenia was characterized by a decrease in platelet count
 394 during the dosing period (days 1 to 11) and a return toward baseline during the 10-day rest period during each
 395 treatment cycle. Overall, thrombocytopenia was reported in 36% of patients. Thrombocytopenia was Grade 3 in
 396 24%, ≥Grade 4 in 5%, and serious in 3% of patients, and the event resulted in VELCADE discontinuation in 2% of
 397 patients [see Warnings and Precautions (5.8)]. Thrombocytopenia was reported more often in patients with
 398 multiple myeloma (38%) compared to patients with mantle cell lymphoma (21%). The incidence of ≥Grade 3
 399 thrombocytopenia also was higher in patients with multiple myeloma (32%) compared to patients with mantle cell
 400 lymphoma (11%). [see Warnings and Precautions (5.8)]

401 **Peripheral Neuropathy**

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

406 In the phase 3 multiple myeloma study, among the 87 patients who experienced ≥ Grade 2 peripheral neuropathy,
 407 51% had improved or resolved with a median of 3.5 months from first onset.

408 Among the patients with peripheral neuropathy in the phase 2 multiple myeloma studies that was Grade 2 and led to
 409 discontinuation or was ≥Grade 3, 73% (24 of 33) reported improvement or resolution following VELCADE dose
 410 adjustment, with a median time to improvement of one Grade or more from the last dose of VELCADE of 33 days
 411 [see Warnings and Precautions (5.2)]

412 **Hypotension**

413 The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13% in
 414 patients treated with VELCADE. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 3% and
 415 ≥Grade 4 in <1%. Three percent (3%) of patients had hypotension reported as an SAE, and 1% discontinued due to
 416 hypotension. The incidence of hypotension was similar in patients with multiple myeloma (12%) and those with
 417 mantle cell lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal event. Doses
 418 of antihypertensive medications may need to be adjusted in patients receiving VELCADE. [see Warnings and
 419 Precautions (5.3)]

420 **Neutropenia**

421 Neutrophil counts decreased during the VELCADE dosing period (days 1 to 11) and returned toward baseline
 422 during the 10-day rest period during each treatment cycle. Overall, neutropenia occurred in 17% of patients and was
 423 Grade 3 in 9% of patients and ≥Grade 4 in 3%. Neutropenia was reported as a serious event in <1% of patients and
 424 <1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple
 425 myeloma (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥Grade 3 neutropenia
 426 also was higher in patients with multiple myeloma (14%) compared to patients with mantle cell lymphoma. (4%).
 427 [see Warnings and Precautions (5.8)]

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

429 Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and ≥Grade 4 in <1% of
 430 patients. Four percent (4%) of patients discontinued treatment due to asthenia. Asthenic conditions were reported in
 431 62% of patients with multiple myeloma and 72% of patients with mantle cell lymphoma.

432 ***Pyrexia***

433 Pyrexia (>38°C) was reported as an adverse event for 34% of patients. The event was Grade 3 in 3% and ≥Grade 4
 434 in <1%. Pyrexia was reported as a serious adverse event in 6% of patients and led to VELCADE discontinuation in
 435 <1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (37%) compared to
 436 patients with mantle cell lymphoma (19%). The incidence of ≥Grade 3 pyrexia was 3% in patients with multiple
 437 myeloma and 1% in patients with mantle cell lymphoma.

438 ***Reactivation of Herpes Virus Infection***

439 Reactivation of herpes virus infections, including herpes zoster and herpes simplex was reported in 13% and 7% of
 440 patients, respectively. This included ophthalmic herpes zoster and ophthalmic herpes simplex each in <1% of
 441 patients. Multidermatomal herpes zoster also has been reported. Herpes reactivation was reported as a serious event
 442 in 2% of patients and led to discontinuation of VELCADE in <1% of patients. In the phase 3 multiple myeloma
 443 study, herpes reactivation was more common in patients treated with VELCADE (13% herpes zoster, 8% herpes
 444 simplex) than in patients treated with dexamethasone (5% herpes zoster, 5% herpes simplex). In the postmarketing
 445 experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have been reported.

446 ***Additional Adverse Events from Clinical Studies***

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

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

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

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

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

456 ***Gastrointestinal disorders:*** Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis,
 457 hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small
 458 intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae,
 459 gastroesophageal reflux

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

462 ***Hepatobiliary disorders:*** Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis,
 463 liver failure

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

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

468 ***Injury, poisoning and procedural complications:*** Catheter related complication, skeletal fracture, subdural
 469 hematoma

470 ***Metabolism and nutrition disorders:*** Hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia,
 471 hypernatremia

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

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

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

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

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

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

485 **6.2 Postmarketing Experience**

486 The following adverse drug reactions have been identified from spontaneous reports during the worldwide post-
 487 marketing experience with VELCADE. Because these reactions are reported voluntarily from a population of
 488 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug
 489 exposure: atrioventricular block complete, cardiac tamponade, ischemic colitis, encephalopathy, dysautonomia,
 490 deafness bilateral, disseminated intravascular coagulation, hepatitis, acute pancreatitis, acute diffuse infiltrative
 491 pulmonary disease, toxic epidermal necrolysis, herpes meningoencephalitis and ophthalmic herpes.

492 **7 DRUG INTERACTIONS**

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

494 Patients who are concomitantly receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450
 495 3A4 should be closely monitored for either toxicities or reduced efficacy.

496 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC₅₀
 497 values of >30µM (>11.5µg/mL). Bortezomib may inhibit 2C19 activity (IC₅₀ = 18 µM, 6.9 µg/mL) and increase
 498 exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450
 499 3A4 and 1A2 in primary cultured human hepatocytes.

500

501 **8 USE IN SPECIFIC POPULATIONS**

502 **8.1 Pregnancy**

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

504 **8.3 Nursing Mothers**

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

509 **8.4 Pediatric Use**

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

511 **8.5 Geriatric Use**

512 Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125
 513 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm. Median time to progression and median
 514 duration of response for patients ≥65 were longer on VELCADE compared to dexamethasone [5.5 mo versus 4.3
 515 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥65
 516 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4
 517 events was 64%, 78% and 75% for VELCADE patients ≤50, 51-64 and ≥65 years old, respectively. [see *Adverse*
 518 *Reactions (6.1); Clinical Studies (14)*]

519 No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients
 520 receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

521 **8.6 Patients with Renal Impairment**

522 The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing
 523 adjustments are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE
 524 concentrations, the drug should be administered after the dialysis procedure. [see *Clinical Pharmacology (12.3)*]

525 8.7 Patients with Hepatic Impairment

526 No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment. [see *Warnings*
 527 *and Precautions (5.10)*]

528 8.8 Patients with Diabetes

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

532 10 OVERDOSAGE

533 There is no known specific antidote for VELCADE overdose [see *Warnings and Precautions (5.3) and Dosage*
 534 *and Administration (2.3)*]. In humans, fatal outcomes following the administration of more than twice the
 535 recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic
 536 hypotension and thrombocytopenia. In the event of an overdose, the patient's vital signs should be monitored and
 537 appropriate supportive care given.

538 Studies in monkeys and dogs showed that IV bortezomib doses as low as 2 times the recommended clinical dose on
 539 a mg/m² basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog
 540 studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of
 541 3.0 mg/m² and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1
 542 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

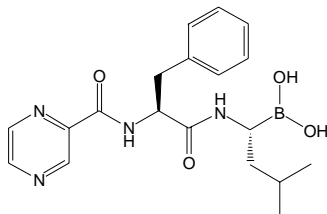
543 11 DESCRIPTION

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

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

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

552 Bortezomib has the following chemical structure:



553
 554 The molecular weight is 384.24. The molecular formula is C₁₉H₂₅BN₄O₄. The solubility of bortezomib, as the
 555 monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

556 12 CLINICAL PHARMACOLOGY

557 12.1 Mechanism of Action

558 Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells.
 559 The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome
 560 pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining
 561 homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect
 562 multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell

563 death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*.
564 Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma.

565 12.2 Pharmacodynamics

566 Following twice weekly administration of 1 mg/m² and 1.3 mg/m² bortezomib doses (n=12 per each dose level), the
567 maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 minutes after
568 drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and 1.3
569 mg/m² doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m² and 1.3 mg/m²
570 dose regimens, respectively.

571 12.3 Pharmacokinetics

572 Following intravenous administration of 1 mg/m² and 1.3 mg/m² doses to 24 patients with multiple myeloma (n=12,
573 per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1)
574 were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum
575 observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m² dose and 89 to 120 ng/mL for the 1.3
576 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after
577 the 1 mg/m² dose and 76 to 108 hours after the 1.3mg/m² dose. The mean total body clearances was 102 and 112
578 L/h following the first dose for doses of 1 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h
579 following subsequent doses for doses of 1 and 1.3 mg/m², respectively.

580 **Distribution:** The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m² following
581 single- or repeat-dose administration of 1 mg/m² or 1.3mg/m² to patients with multiple myeloma. This suggests
582 bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged
583 83% over the concentration range of 100 to 1000 ng/mL.

584 **Metabolism:** *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes
585 indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2.
586 Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to
587 form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated
588 bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and
589 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

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

591 **Age:** Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received
592 intravenous doses of 1 mg/m² and 1.3 mg/m² showed that both dose-normalized AUC and C_{max} tend to be less in
593 younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max}
594 than those ≥ 65 years of age (n=13).

595 **Gender:** Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17)
596 patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m² doses.

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

598 **Hepatic Impairment:** No pharmacokinetic studies were conducted with bortezomib in patients with hepatic
599 impairment [*See Warnings and Precautions (5.10)*].

600 **Renal Impairment:** A pharmacokinetic study was conducted in patients with various degrees of renal impairment
601 who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl
602 ≥60 mL/min/1.73 m², N=12), Mild (CrCl=40-59 mL/min/1.73 m², N=10), Moderate (CrCl=20-39 mL/min/1.73 m²,
603 N=9), and Severe (CrCl < 20 mL/min/1.73 m², N=3). A group of dialysis patients who were dosed after dialysis
604 was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m² of
605 bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the
606 groups. [*See Specific Populations (8.6)*]

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

608 13 NONCLINICAL TOXICOLOGY

609 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

610 Carcinogenicity studies have not been conducted with bortezomib.

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

614 Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in
615 the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at
616 doses ≥ 0.3 mg/m² (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at
617 1.2 mg/m². VELCADE could have a potential effect on either male or female fertility.

618 **13.2 Animal Toxicology**

619 *Cardiovascular Toxicity:* Studies in monkeys showed that administration of dosages approximately twice the
620 recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension,
621 bradycardia, and death 12 to 14 hours post dose. Doses ≥ 1.2 mg/m² induced dose-proportional changes in cardiac
622 parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a
623 repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also
624 observed.

625 *Chronic Administration:* In animal studies at a dose and schedule similar to that recommended for patients (twice
626 weekly dosing for 2 weeks followed by 1-week rest), toxicities observed included severe anemia and
627 thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of
628 bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots,
629 and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were
630 observed.

631 **14 CLINICAL STUDIES**

632 **14.1 Multiple Myeloma**

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

634 A prospective phase 3, international, randomized (1:1), stratified, open-label clinical study enrolling 669 patients
635 was designed to determine whether VELCADE resulted in improvement in time to progression (TTP) compared to
636 high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients
637 considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline grade ≥ 2
638 peripheral neuropathy or platelet counts $< 50,000/\mu\text{L}$. A total of 627 patients were evaluable for response.

639 Stratification factors were based on the number of lines of prior therapy the patient had previously received (1
640 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during
641 or within 6 months of stopping their most recent therapy versus relapse > 6 months after receiving their most recent
642 therapy), and screening β_2 -microglobulin levels (≤ 2.5 mg/L versus > 2.5 mg/L).

643 Baseline patient and disease characteristics are summarized in **Table 5**.

644
645**Table 5: Summary of Baseline Patient and Disease Characteristics
in the Phase 3 Multiple Myeloma Study**

Patient Characteristics	VELCADE N=333	Dexamethasone N=336
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤ 70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10 ⁹ /L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β_2 -microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤ 30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
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%

646 Patients in the VELCADE treatment group were to receive eight 3-week treatment cycles followed by three 5-week
647 treatment cycles of VELCADE. Patients achieving a CR were treated for 4 cycles beyond first evidence of CR.
648 Within each 3-week treatment cycle, VELCADE 1.3 mg/m²/dose alone was administered by IV bolus twice weekly
649 for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment
650 cycle, VELCADE 1.3 mg/m²/dose alone was administered by IV bolus once weekly for 4 weeks on Days 1, 8, 15,
651 and 22 followed by a 13-day rest period (Days 23 to 35) [see *Dosage and Administration(2.1)*].

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

658 Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients
659 randomized to dexamethasone were offered VELCADE, regardless of disease status. At this time of study
660 termination, a final statistical analysis was performed. Due to this early termination of the study, the median
661 duration of follow-up for surviving patients (n=534) is limited to 8.3 months.

662 In the VELCADE arm, 34% of patients received at least one VELCADE dose in all 8 of the 3-week cycles of
663 therapy, and 13% received at least one dose in all 11 cycles. The average number of VELCADE doses during the

664 study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all 4
665 of the 5-week treatment cycles of therapy, and 6% received at least one dose in all 9 cycles.

666 The time to event analyses and response rates from the phase 3 multiple myeloma study are presented in **Table 6**.
667 Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT)
668 criteria.¹ Complete response (CR) required <5% plasma cells in the marrow, 100% reduction in M-protein, and a
669 negative immunofixation test (IF⁻). Partial Response (PR) requires ≥50% reduction in serum myeloma protein and
670 ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with
671 stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for
672 complete response including 100% reduction in M-protein by protein electrophoresis, however M-protein was still
673 detectable by immunofixation (IF⁺).

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

675 ^a Kaplan-Meier estimate.

676 ^b Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A
677 hazard ratio less than 1 indicates an advantage for VELCADE.

678 ^c p-value based on the stratified log-rank test including randomization stratification factors.

679 ^d Precise p-value cannot be rendered.

680 ^e Response population includes patients who had measurable disease at baseline and received at least 1 dose of
681 study drug.

682 ^f EBMT criteria¹; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria, nCR is in the PR
683 category.

684 ^g In 2 patients, the IF was unknown.

685 ^h p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the
686 stratification factors;

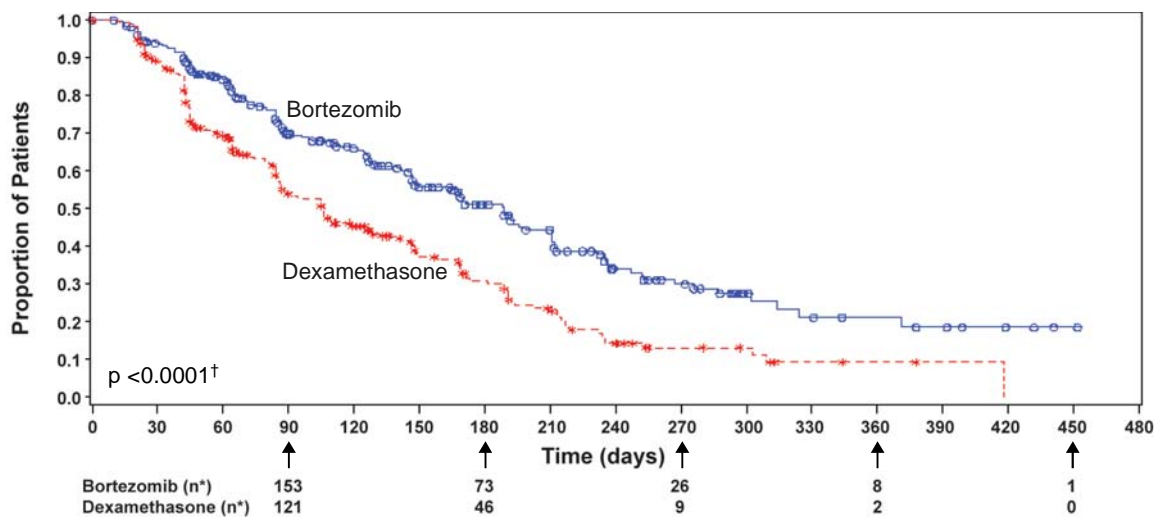
687 ⁱ Not Estimable.

688 ^j Not Applicable, no patients in category.

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

690
691

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



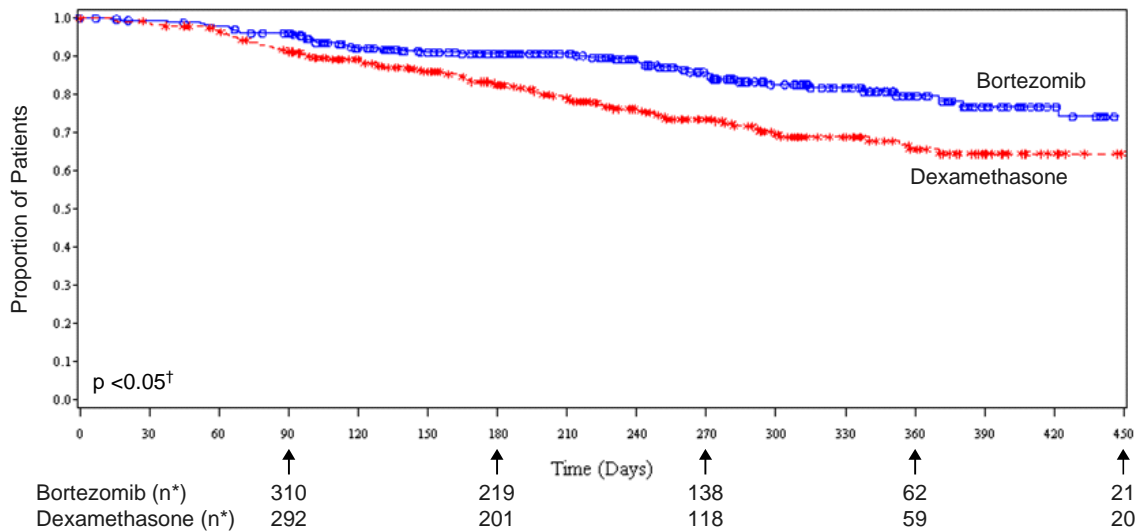
* Patients remaining after the indicated timepoint
† p-value from log-rank test

692

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

695
696

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



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

697

698 For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months
699 (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the
700 dexamethasone arm. The response rate was significantly higher on the VELCADE arm regardless of β_2 -
701 microglobulin levels at baseline.

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

703 An open-label, multicenter study randomized 54 patients with multiple myeloma who had progressed or relapsed on
704 or after front-line therapy to receive VELCADE 1 mg/m² or 1.3 mg/m² IV bolus twice weekly for 2 weeks on Days
705 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). The median duration of time between diagnosis of
706 multiple myeloma and first dose of VELCADE on this trial was 2.0 years, and patients had received a median of 1
707 prior line of treatment (median of 3 prior therapies). A single complete response was seen at each dose. The overall
708 response rates (CR + PR) were 30% (8/27) at 1 mg/m² and 38% (10/26) at 1.3 mg/m².

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

710 Patients from the two phase 2 studies who in the investigators' opinion would experience additional clinical benefit
711 continued to receive VELCADE beyond 8 cycles on an extension study. Sixty-three (63) patients from the phase 2
712 multiple myeloma studies were enrolled and received a median of 7 additional cycles of VELCADE therapy for a
713 total median of 14 cycles (range 7 to 32). The overall median dosing intensity was the same in both the parent
714 protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or
715 higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard
716 3-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed
717 with prolonged VELCADE treatment. [see Adverse Reactions(6.1)]

718 **14.2 Mantle Cell Lymphoma**

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

720 The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-
721 label, single-arm, multicenter study of 155 patients with progressive disease who had received at least 1 prior
722 therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were caucasian. Of the
723 total, 75% had one or more extra-nodal sites of disease, and 77% were stage 4. In 91% of the patients, prior therapy
724 included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty
725 seven percent (37%) of patients were refractory to their last prior therapy. An IV bolus injection of VELCADE 1.3
726 mg/m²/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period
727 (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for 4 cycles
728 beyond first evidence of CR or CRu. The study employed dose modifications for toxicity. [see Dosage and
729 Administration (2.2)]

730 Responses to VELCADE are shown in **Table 9**. Response rates to VELCADE were determined according to the
731 International Workshop Response Criteria (IWRC)² based on independent radiologic review of CT scans. The
732 median number of cycles administered across all patients was 4; in responding patients the median number of cycles
733 was 8. The median time to response was 40 days (range 31 to 204 days). The median duration of follow-up was
734 more than 13 months.

735 **Table 9: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study**

Response Analyses (N = 155)	N (%)	95% CI
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)
Duration of Response	Median	95% CI
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)

736 **15 REFERENCES**

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749

750 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

753 NDC 63020-049-01
754 3.5 mg single use vial

755 Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15 to 30°C
756 (59 to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

757 Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic drugs, including the use
758 of gloves and other protective clothing to prevent skin contact³⁻⁶.

759


760 **Caution: R_x only**

761 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

762 ***Distributed and Marketed by:***

763 Millennium Pharmaceuticals, Inc.
764 40 Landsdowne Street
765 Cambridge, MA 02139

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771 **17 PATIENT COUNSELING INFORMATION**

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

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

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

780 **PATIENT INFORMATION**

781 VELCADE® (bortezomib) for Injection is intended for use under the guidance and supervision of a healthcare
782 professional. Please discuss the possibility of the following side effects with your doctor:

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

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

787 ***Pregnancy/Nursing:***

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

793 ***Dehydration/Hypotension:***

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

798 ***Concomitant Medications:***

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

801 ***Diabetic Patients:***

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

804 ***Peripheral Neuropathy:***

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

807 ***Herpes zoster (Shingles):***

808 Contact your doctor if you develop a rash.

809 ***Heart Failure and Lung Disease:***


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

811 ***Other Information:***

812 Please contact your doctor if you experience a convulsion, persistent headache, reduced eyesight or an increase in
813 your blood pressure.

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